CLINICAL SYMPTOMS, SOCIAL AND ROLE FUNCTIONING, LONGER-TERM CORTISOL LEVELS, AND BRAIN ACTIVATION DURING WORKING MEMORY AND REST IN THE EARLY STAGES OF MENTAL HEALTH PROBLEMS

by

KAREEN HEINZE

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College of Life and Environmental Sciences

University of Birmingham

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ABSTRACT

Mental disorders are associated with a range of neurobiological abnormalities, including hormonal disturbances and brain changes. However, most of the research has been conducted in established and even chronic mental health conditions. Recently, clinical staging models have emerged, aiming to guide treatment selection relevant to stage and progression of illness. Whereas clinical staging has established itself for the psychosis continuum, less is known about staging in other disorders such as depression, mania, anxiety, substance use, and eating disorders. This thesis looked at the early stages of mental disorders in general, and specifically at the ultra-high risk state for psychosis. 73 help-seeking youths aged 16-26 years were interviewed for clinical symptomatology and social and role functioning, and followed up after 3 and 6 months. Neurobiological assessments were additionally undertaken in a subset of those clinical participants (n = 35), and healthy controls (HC, n = 35), involving hair cortisol analyses, and brain imaging during working memory processes and rest. Significantly increased hair cortisol levels, and brain hypo-activation during working memory processes and subtly decreased resting-state brain connectivity were discovered in clinical participants as compared to HC. Early mental health problems appear to have some neurobiological manifestations, however, larger cohort studies with multiple follow-up assessments over an extended time period are needed to replicate findings and to draw firm conclusions addressing clinical practice.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ACC – anterior cingulate cortex
ANCOVA – analyses of covariance
ANOVA – analyses of variance
APS – attenuated psychotic symptoms
ASSIST – Alcohol, Smoking and Substance Involvement Screening Test
BAR – Bipolar at-risk
BL – baseline
BLIPS – brief limited intermittent psychotic symptoms
BOLD – blood-oxygenation level-dependent
CAARMS – Comprehensive Assessment of At-Risk Mental States
CBT – Cognitive-behavioural therapy
CTQ(-SF) – childhood trauma questionnaire (short form)
dlPFC – dorsolateral prefrontal cortex
DMN – default-mode network
DSM – Diagnostic and Statistical Manual of Mental Disorders
ECN – Executive-control network
FEP – first episode of psychosis
fMRI – functional magnetic resonance imaging
FP – fronto-parietal
FWHM – full width at half maximum
FWE – family-wise error
GAD – generalised anxiety disorder
HC – healthy controls
HPA – hypothalamus-pituitary-adrenal
HPG – hypothalamus-pituitary-gonadal
IC – independent component
ICA – Independent Component Analysis
ICD – International classification of diseases
IFG – inferior frontal gyrus
K-10 – Kessler Psychological Distress Scale
M – mean
MD – major depression
MELODIC – Multivariate Exploratory Linear Optimised Decomposition into Independent Components
MNI - Montreal Neurological Institute
mPFC – medial prefrontal cortex
MRI – magnetic resonance imaging
OASIS – Overall Anxiety Severity and Impairment Scale
PACE – Personal Assessment and Crisis Evaluation
PCC – posterior cingulate cortex
PFC – prefrontal cortex
PLE – psychotic-like experiences
PSS – Perceived Stress Scale
PTSD – Post-traumatic stress disorder
QIDS – Quick Inventory of Depressive Symptoms
ROI – region of interest
rs-fMRI – resting-state functional magnetic resonance imaging
SN – salience network
SCID – Structured Clinical Interview for DSM disorders
SD – standard deviation

SFG – superior frontal gyrus
SIPN – social information processing network
SMG – supramarginal gyrus
SOFAS – Social and Occupational Functioning Assessment Scale
STG – superior temporal gyrus
TNN – task-negative network
TPN – task-positive network
TFCE – threshold-free cluster enhancement
UHR – ultra-high risk

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CHAPTER ONE

LITERATURE REVIEW

Mental illnesses, such as schizophrenia and depression are constituting 13% of the global burden of disease, outreaching cancer and cardiovascular disease (Collins et al., 2011). With 75% of mental illnesses starting before the age of 24 (Kessler et al., 2005), health systems, researchers and clinicians aspire to understand and improve especially youth mental health (Shah, 2015), questioning parameters by which mental health is defined at the moment. Stepping away from conventional Diagnostic and Statistical Manual of Psychiatric Disorders (DSM) and the International Classification of Diseases (ICD) diagnoses, by utilising a dimensional approach and clinical staging in mental disorders (McGorry et al., 2007), is thought to more efficiently detect and treat mental health problems. The idea of risk syndromes for mental disorders (especially in the field of psychosis and bipolar disorder) has emerged, for an early detection and intervention to delay, ameliorate or prevent threshold disorders (McGorry et al., 2007). Even though being a promising approach with good evidence for its utility, new challenges have emerged, e.g. whether this risk syndrome was to be included as diagnostic category in the DSM (Yung, Nelson, Thompson, & Wood, 2010), how important psychosocial functioning actually is as predictor and outcome variable, and how clinical staging can be implemented for disorders other than psychosis and bipolar disorder.

This thesis looks at youth mental health and therefore the early stages of mental health problems in help-seeking adolescents and young adults. Even though there have been some recent attempts to look at the role of neurobiological variables in the development of mental health problems (e.g., Lagopoulos, Hermens, Naismith, Scott, & Hickie, 2012; Lagopoulos et al., 2013), generally only little research has been conducted in this field to look at underlying biological mechanisms. This thesis therefore included working

memory as a key executive function and functional intrinsic brain connectivity, and cortisol levels as stress marker. The aims are to explore:

- how depressive, psychotic and anxiety symptoms are related to each other and social and occupational functioning, observed over a period of six months,

- how longer-term stress links in with mental health symptoms as measured by means of hair cortisol analyses,

- if brain activity during working memory processes is altered in individuals with early mental health problems,

- if connectivity of brain networks during rest is altered in individuals with early mental health problems,

- and whether there is an association between brain function and longer-term cortisol levels,

focusing on depressive, psychotic and anxiety symptoms due to the comparatively high prevalence in the current sample.

This literature review gives an overview about youth mental health and the importance of the period of adolescence and early adulthood for the development of psychiatric disorders, also by looking at underlying neurobiological mechanisms (Section 1.1). Epidemiological, clinical and neurobiological findings for most common mental disorders (affective, psychotic, anxiety, eating, and substance use disorders) and their risk syndromes and risk factors, and how mental health symptoms interact with each other, are described in Section 1.2. Section 1.3 describes different approaches to mental health and issues that are associated with these approaches respectively, and Section 1.4 how clinical and functional outcomes can be improved, followed by Section 1.5 which gives an outlook of the thesis.

1.1 Youth mental health and development of psychiatric disorders

Adolescence is defined as the "gradual period of transition from childhood to adulthood" (Spear, 2000), which includes puberty – the period where sexual maturity takes place (Sinclair, Purves-Tyson, Allen, & Weickert, 2014). The foundations of future patterns of adult health are laid during adolescence; health in adolescence is in turn the product of interactions between the development during prenatal development and childhood, and changes in biology and social and role demands that come along with puberty (Sawyer et al., 2012). This period of adolescence and young adulthood is furthermore characterised by a greatly increased vulnerability for the development of mental disorders, with half of the lifetime cases of mental disorders starting by age 14 and three quarters by age 24 (Kessler et al., 2005).

Although puberty can be seen as a biological marker for the onset of adolescence, adolescence constitutes a vague concept, considering its differential definition across cultures worldwide (Patel, Flisher, Hetrick, & McGorry, 2007). Patel et al. (2007) questioned the validity of the notion of adolescence, and alternatively suggested to separately consider the developmental and health needs of children (<12 years) and young people (12-24 years) instead. This differentiation may be more useful in terms of looking at youth mental health and its underlying neurobiological mechanisms, however, for the purpose of this literature review such a distinction cannot be made, because existing - for this thesis relevant - literature mainly focuses on and defines very heterogeneous age groups. Relevant studies, comprising older aged children up to early adulthood will be reported.

Overall prevalence rates for mental disorders in children and youths are an estimated 15% (for review, see Waddell & Shepherd, 2002), with lifetime prevalence estimates being 3% for psychotic disorders (Peraala et al., 2007), 29% for anxiety disorders, 21% for mood disorders, and 15% for substance use disorders (Kessler et al., 2005). Median age of onset for schizophrenia was 23 years (Kessler et al., 2007), for anxiety at age 11, for substance use at age 20 and for mood disorders at age 30 (Kessler et al., 2005). McGorry, Goldstone,

Parker, Rickwood, and Hickie (2014) summarise that prevalence rates of mental disorders in youths are further documented to be the highest of all age groups.

Patel et al. (2007) describe mixed evidence for whether prevalence of mental disorders in youths have increased in recent decades. Evidence, e.g. for depressive disorder is mixed, with some studies indicating increases, however, those studies are based on recall data, and older people have the tendency to forget episodes from their younger years. A meta-analysis that addressed this issue, showed no evidence to support the claim of an increase (Patel et al., 2007). Multifactorial causes for the development of mental disorders in young people have been well supported in the literature; risk and protective factors are illustrated in Table 1.1 by domain. Various risk factors have been proposed (e.g. growing up in environments with parents with mental disorders, parental conflict or separation, violence, child abuse, substance use), often suggesting complex pathways of their association with mental health outcomes. It should, however, be emphasised that a considerable proportion of those individuals facing severe adversities and multiple risk factors, do not develop mental disorders, since protective factors can modify and eliminate the effect of risk factors. Amongst others, appear social support and adequate psychosocial stimulation during early childhood, to be important in promoting mental health (Patel et al., 2007).

Table 1.1
Risk and protective factors of mental health in youths (in Patel et al., 2007)

	Risk factors	**Protective factors**
Biological	Exposure to toxins (e.g., tobacco, alcohol) in pregnancy Genetic tendency to psychiatric disorder Head trauma Hypoxia at birth and other birth complications HIV infection Malnutrition Substance abuse Other illnesses	Age-appropriate physical development Good physical health Good intellectual functioning
Psychological	Learning disorders Maladaptive personality traits Sexual, physical, emotional abuse and neglect Difficult temperament	Ability to learn from experiences Good self-esteem High level of problem-solving ability Social skills
Social		
Family	Inconsistent care-giving Family conflict Poor family discipline Poor family management Death of a family member	Family attachment Opportunities for positive involvement in family Rewards for involvement in family
School	Academic failure Failure of schools to provide appropriate environment to support attendance and learning Inadequate or inappropriate provision of education Bullying	Opportunities for involvement in school life Positive reinforcement from academic achievement Identity with school or need for educational attainment
Community	Transitions (e.g., urbanisation) Community disorganisation Discrimination and marginalisation Exposure to violence	Connectedness to community Opportunities for leisure Positive cultural experiences Positive role models Rewards for community involvement Connection with community Organisations

Risk factors play an important role for understanding the psychopathology of mental disorders; when connecting certain risk characteristics, so-called "risk syndromes" emerge. Individuals with these *risk syndromes* or *sub-threshold disorders* are at increased risk for transitioning to similar or different threshold disorders (Shah, 2015). Early intervention and staged treatment (see Section 1.4.2) might help reduce disability and morbidity, however, this requires identification of risk syndromes (Ratheesh et al., 2015). Risk syndromes for

psychosis have been extensively studied in the past decades (see Section 1.2.2), and literature on other risk syndromes, e.g. for bipolar disorder, and on sub-threshold depression (see Section 1.2.1), anxiety (see Section 1.2.3), and eating disorders (see Section 1.2.4) have started to arise and will be discussed under the respective chapters.

Another concept, which is very useful in understanding youth mental health, is that of *developmental epidemiology* - which aims to integrate developmental psychopathology into epidemiology. The overall goal is to understand how developmental processes affect the risk for mental disorders, to ultimately propose preventive and early intervention strategies according to the stage of risk (Patel et al., 2007). This is of high importance because youth is the period where social, psychological, academic, and occupational pathways are laid down, and even mild and brief episodes can seriously disable and block young people's potential, possibly even leading to circles of dysfunction and disadvantage which can be difficult to reverse. Psychopathology in young people plays an important role in limiting social and economic participation, extending into adult life, however, improving youth mental health can significantly reduce unemployment and dependency from state benefits (McGorry, Purcell, Hickie, & Jorm, 2007; Patel et al., 2007).

Young people present with comparatively high rates of suicide and self-harm, and a strong association exists between poor mental health and other health and developmental concerns such as academic achievements, use and misuse of substances, violence and sexual health (Patel et al., 2007). In particular, depressed adolescents were found to show more adverse behaviours such as cigarette smoking, substance use, conduct disorders, and problems at school (including drop-out) (Keyes, 2006). Keyes (2006) argues that depressed youths are not mentally healthy, however, the reverse is not true by implying that youths without depression and other mental illness are healthy, and that health can be defined as the absence of illness and malfunctioning. There is no standard for how to measure the presence of mental health. In the past decades, science has portrayed it by default as the absence of psychopathology. This position has been rested on the assumption that mental illness and health are dichotomous, forming a single bipolar dimension. This simplification

comes with certain issues, e.g. individuals who are free of mental disorder, may not feel healthy or function well (Keyes, 2005).

The assessment of positive mental health, that is, positive feelings towards one's self, and functioning well in life, has therefore been translated into markers of developmental success in youth, with main findings being that depressive symptoms and conduct problems (e.g. arrest, school absence, substance use) decreased, and psychosocial functioning improved (more positive self-concept, being closer to others, better school integration) as mental health increased (Keyes, 2006).

The importance of considering subjective wellbeing in the context of adolescent mental health has been supported by evaluating a dual-factor model in early adolescence, which proposes to assess positive indicators of wellbeing, additionally to traditional negative indicators such as psychopathology (Suldo & Shaffer, 2008). Subjective wellbeing consists of 3 components: life satisfaction, positive and negative affect. This includes the appraisal of one's happiness with global and domain-specific aspects of life (e.g. family, school), a positive judgement of one's quality of life and a more frequent experience of positive relative to negative affect. The identification of four groups supported the existence of this dual-factor model: 57% of youths were considered to have "complete mental health" (high wellbeing, low psychopathology), 13% were "vulnerable" (low wellbeing, low psychopathology), 13% "symptomatic but content" (high wellbeing, high psychopathology), and 17% "troubled" (low wellbeing, high psychopathology), with means for academic outcome, physical health, and social functioning significantly differing between the four groups. The importance of high wellbeing was emphasised as only adolescents in the "complete mental health" group demonstrated optimal functioning (Suldo & Shaffer, 2008). This also emphasises the importance of looking at youth mental health not only from the viewpoint of classifying into psychopathological categories (see Section 1.3.1), but by looking at other relevant factors such as wellbeing and contentment, despite experiencing mental health problems.

1.1.1 Development of the brain and endocrine system during adolescence

Adolescence and early adulthood are often associated with the onset of mental disorders due to the occurrence of biological, psychological and sociological reasons. In addition to ordinary risk factors (such as family history and temperament) that apply across the life span, occur risk factors that are specific for this time period of adolescence (e.g. challenges that are associated with gaining independence from parents and being self-sufficient, and with academic success and establishing social relationships outside of the family), as well as biological changes in the adolescent brain and endocrine system. Typical developmental processes of the healthy maturing brain during adolescence and early adulthood shall be described in this section, to understand the neurobiology of psychopathological processes of mental disorders in youth, which will be provided consequently (see Section 1.1.2).

Amongst those biological reasons are dynamic changes in brain structure and function, resulting in a refinement of neural circuits (McGorry et al., 2014). Keshavan, Giedd, Lau, Lewis, and Paus (2014) reviewed brain changes during adolescence, and stated that whereas continuing myelination is leading to white matter volume increases from childhood to early adulthood, cortical thickness, e.g. in the dorsal medial prefrontal cortex (PFC) and temporo-parietal junction has been found to decrease - that is, in regions which are important for the development of social cognition (Van Overwalle, 2009). Adolescence is not only a period that is associated with volumetric brain changes: adequate functional connectivity is further important for social-emotional processing (Keshavan et al., 2014). Increases in functional connectivity between those regions during adolescence give further insight into enhanced social and emotional understanding and responses in youth with increasing age. This is an important development because social relationships are especially relevant in the period of adolescence for developing and consolidating one's (social) identity, and to take one another's perspective to successfully communicate (Choudhury, Blakemore, & Charman, 2006).

Refinement of neurochemical pathways happens via a synaptic reorganisation during adolescence (e.g. in the dorsolateral PFC), increasing the efficiency of cognitive systems (Choudhury et al., 2006). Efficiency has various specific definitions when considering the connectivity of the brain (e.g. global and local efficiency, see Bullmore & Sporns, 2009); however, high efficiency generally means that closely adjacent brain areas form local clusters which are specialised in certain brain functions but also that brain areas which are segregated by greater distance are well connected to communicate effectively (van den Heuvel, Stam, Kahn, & Hulshof Pol, 2009). For example, higher cognitive functions such as working memory, activate local clusters in various regions of the prefrontal cortex, but are also connected to parietal regions in functional magnetic resonance imaging (fMRI) studies (e.g. Owen et al., 2005, see Chapter 5).

This elimination of specific synapses (= pruning) is possibly associated with the neurons' experience-related plasticity. Selective attention, for example, may improve due to pruning of glutamatergic synapses by reducing the number of distractors from childhood to early adolescence (Keshavan et al., 2014). This means, older children and adolescents will be better able to focus and attend to few, but relevant stimuli, whereas younger children may be overwhelmed by attempting to simultaneously process a large number of stimuli, due to their brain's inability to filter relevant information from the wealth of internal and external stimuli. Changes in limbo-cortical dopamine balance, that further occur during this period, might in part be responsible for risk taking behaviour, mood, substance use and psychotic disorders (Keshavan et al., 2014).

Due to age-dependent volume increases of the pituitary gland as key structure of the hypothalamus-pituitary-gonadal (HPG) and hypothalamus-pituitary-adrenal (HPA) axis, a rise of gonadal and stress hormones takes place during adolescence. This pituitary volume increase is probably the result of stimulating effects of gonadotropin- (and corticotropin-) releasing hormones synthesised in the hypothalamus, and feedback effects from circulating gonadal (and adrenal) hormones on the pituitary (Keshavan et al., 2014). Increasing levels of testosterone (in men) and fluctuating female gonadal hormones (during the menstrual

cycle and as found in contraceptive hormones) were thought to affect brain structure and function during adolescence, e.g. contributing to decreases of cortical grey matter (Keshavan et al., 2014). Whilst adolescence is a time of high stress reactivity and the stress response of the HPA axis is maturing, gonadal hormones and glucocorticoids have been shown to affect dopaminergic neurotransmission in specific brain areas (e.g. striatum, PFC), and are therefore proposed to be implicated in cognitive and affective processes during adolescence (Keshavan et al., 2014). Further, the maturing brain is well fitted with hormone receptors and conversion enzymes to respond to sex and stress hormones, and therefore adolescence can be characterised by an increasing responsiveness for gonadal and adrenal hormones in cortical brain regions (e.g. especially in the temporal lobe for sex hormones, and PFC for stress hormones) (Sinclair et al., 2014).

1.1.2 Adolescence and Psychopathology

Keshavan et al. (2014) state that imbalances or deviations in the developmental processes of the brain and endocrine system increase the risk for mental illnesses in youth. Those biological peri-adolescent risk factors were found - together with psychosocial factors (e.g. school, relationships) (Paus, Keshavan, & Giedd, 2008), genetic and environmental risk factors - to be involved in the pathogenesis of psychotic and mood disorders (Keshavan et al., 2014). A dysmaturation of neural connectivity during adolescence, is an important part of the pathophysiology of psychotic disorders, which leads to an imbalance of excitatory and inhibitory systems and to constraint of neuronal plasticity. This involves dopaminergic and glutamatergic synapses of neural circuits that are associated with executive, affective, and social functions. Similarly, adolescents with bipolar disorder and those at risk, display dysfunction of emotion regulation (PFC, amygdala, hippocampus) and reward (PFC, striatum) circuits (Keshavan et al., 2014).

Advanced pubertal status has repeatedly been linked to psychopathology. E. g., larger pituitary volumes (as key component of the HPA and HPG axis, see Section 1.1.1),

and higher depressive symptoms cross-sectionally were predicted by early pubertal timing, and mediated longitudinally the association between early pubertal timing and higher depressive symptoms (Whittle et al., 2012). These findings support the idea of neurobiological mechanisms being responsible for linking pubertal timing and depressive symptoms (Simmons et al., 2014). The evidence for the association between advanced pubertal status and anxiety symptoms is, however, mixed: A review concluded that whereas there is only limited and very little evidence for girls, more consistent associations were observed for boys (e.g. for testosterone) (Reardon, Leen-Feldner, & Hayward, 2009). Findings for cortisol and anxiety symptoms were similarly inconsistent, e.g. positive correlations amongst girls but not boys, but no association of pubertal status and cortisol levels after biological challenge (carbon-dioxide inhalation) in youths with anxiety or mood disorder, were found (Reardon et al., 2009). Further, pubertal status and tempo at age 12 significantly predicted substance use problems in mid to late adolescence, partially mediated by high sensation seeking and low impulse control (Castellanos-Ryan, Parent, Vitaro, Tremblay, & Seguin, 2013).

Nelson, Leibenluft, McClure, and Pine (2005) speculated that the dysregulation of the social information processing network (SIPN) might be involved in the development of mood and anxiety disorders during adolescence. A network is a system of interconnected sets of brain regions (*nodes*) that serve specific functions. The SIPN, for example, is a large network that consists of three nodes that each consist of multiple regions. It serves as the name indicates, the processing of socially relevant information. The first node, the detection node, e.g. consists of the inferior occipital cortex, and fusiform gyrus, and is important for perceptual functions and categorising a stimulus as social. The second node, the affective node is composed of areas primarily involved in reward and punishment, such as the ventral striatum and the amygdala, and thirdly, the cognitive-regulatory node is involved in perceiving mental states of others and goal-directed behaviour, and is anchored in e.g. paracingulate areas, and dorsal, dorso-medial, and ventral prefrontal cortices. With adolescence being a period of increased emotional responsiveness to social stimuli, and

social cognition playing an important role during adolescence (see Section 1.1.1), development-related changes to this network might be particularly relevant for emergent psychopathology during adolescence: Rapid and drastic changes occur to the affective node with the onset of puberty (e.g. regarding sexual behaviour and the formation of social bonds), whereas the maturation of the cognitive node lags behind by several years. This theory of dysregulation of the SIPN is supported by volumetric alterations of the superior temporal gyrus (STG, which is generally involved in social cognition), ventral PFC (as part of the cognitive-regulatory node) and amygdala (as part of the affective node), alterations of frontal white matter, and of orbitofrontal choline levels in adolescents with mood and anxiety disorders (Nelson et al., 2005).

1.2 Description of major psychological disorders relevant for clinical staging (epidemiology, clinical and neurobiological findings)

Depression, mania, psychotic, anxiety, eating and substance use disorders will be described in the following, concerning their epidemiology, and clinical and neurobiological findings relevant to the outlook of this thesis (e.g. cortisol levels, and neuroimaging findings). The focus is on the period of adolescence and early adulthood due to the ages 16-25 years of the currently investigated sample, however, due to a shortage of relevant literature in this age range, the following description also covers earlier periods such as childhood, or later periods in adulthood. The ultra-high risk (UHR) state of psychosis and bipolar disorder will receive special attention due to their similarity with early mental health problems in general. Even though the aim of this thesis is to look at youth mental health without diagnosing or specifically referring to diagnostic categories, findings are described on the basis of symptom categories in the following. This is due to the vast majority of studies being based on classification systems such as the DSM, and studies using alternative approaches to mental health having only recently emerged (see Section 1.3). Results from the empirical chapters of this thesis will be linked to these reported findings from previous literature by

classifying individuals into a dichotomy of high versus low depressive, psychotic and anxiety symptoms, respectively.

1.2.1 Affective disorders

Depression and mania are common mental disorders in the adolescent general population. Kessler, Avenevoli, and Merikangas (2001) reviewed retrospective reports, demonstrating that 50% of depressive and 90% of mania cases that have their onset during or before adolescence, persist into adulthood. The course of depression is often characterised by high continuity and recurrences when disorder onset takes place in childhood or adolescence, whereas the course of mania is typically characterised by chronicity (Kessler et al., 2001). Recurrence rates in depression are as high as at least 50% for those who have recovered from a first episode, and 80% for those who have recovered from a second episode (American Psychiatric Association, 2000). An early onset of depression was further shown to increase the risk of subsequent substance abuse (Kessler et al., 2001). Thapar, Collishaw, Pine, and Thapar (2012) identified genetic disposition and psychosocial stress as the major risk factors for depression, and sex hormones and early adversity are further increasing the risk for the disorder in adolescents. Depression, in turn, constitutes a strong risk factor for suicide, with half of the suicide cases coinciding with depression at time of the death. Interestingly, a British national survey revealed that risk factors such as biological and economic deprivation early in life (e.g. low birth weight, overcrowding in childhood) were only indirectly associated with depression in adulthood: low birth weight was found to be associated with the intermediate risk factor of developmental delay in infancy, and overcrowding in childhood with the intermediate risk factor of economic deprivation in adulthood. Both intermediate risk factors subsequently showed an association with depression in adulthood (Colman et al., 2014).

Adolescents with bipolar disorder presented with functional impairment, high rates of comorbidity, and suicide attempts (Lewinsohn, Klein, & Seeley, 1995). About 27% of individuals with sub-syndromal depression went on to develop major depression (Fergusson,

Horwood, Ridder, & Beautrais, 2005) within 2 years and 45% of individuals with sub-syndromal bipolar disorder transitioned to threshold disorder within one year (Axelson et al., 2011). A population-based study of 12,000 adolescents reported 29% sub-threshold (and 10% threshold) depression – sub-threshold disorders, likewise to threshold disorders, presenting with high rates of comorbidity, functional impairment and suicidality (Balazs et al., 2013). However, not all young individuals who are presenting with risk factors, develop the disorder: High intelligence, emotion-regulation capacities, coping and thinking styles, and good quality interpersonal relationships have been identified as markers of resilience (Thapar et al., 2012).

Alterations of two interrelated neuronal circuits have been linked with the risk for depression and the disorder itself. A circuit being crucial for the response to danger, that connects the amygdala, hippocampus, PFC and the HPA axis, displayed hyperactivity in adolescents at risk for or diagnosed with major depression (MD) (Thapar et al., 2012). A second circuit, comprising the striatum, PFC and ventral dopamine-based systems, which plays an important role in learning of reward, demonstrates reduced activity in at-risk and depressed individuals (Thapar et al., 2012). Likewise, abnormalities of the PFC, striatum, and amygdala were discovered early in the course of bipolar disorder, and proposed to potentially precede illness onset (Strakowski, DelBello, & Adler, 2005). These changes in brain circuits may provide neurobiological explanations for diverse symptoms and observations in mood disorders such as the reduced ability to think, memory problems, and indecisiveness that might be related to prefrontal abnormalities, high comorbidity with anxiety due to the involvement of the amygdala, and diminished interest and motivation due to reduced involvement of the striatum.

Bipolar at-risk (BAR) state

Due to the highly disabling nature and the likewise high economic burden of bipolar disorder (Bechdolf et al., 2012), early detection and intervention of the BAR state has become a well researched risk syndrome for mental disorders as well, after the at-risk state

for psychosis (Section 1.2.2). BAR criteria are the ages between 15-25 years, and experiencing (1) sub-threshold mania symptoms, (2) minor depression plus hypo-manic features (that is, episodes of depression and mania that do not reach the threshold for major depression and mania), or (3) minor depression plus genetic risk (Bechdolf et al., 2012). There is preliminary evidence for the predictive validity for BAR criteria predicting the onset of mania and hypomania: 14% of individuals meeting BAR criteria transitioned to mania/hypomania within 12 months, as opposed to no one in the non-BAR group (Bechdolf et al., 2014). In a sample of help-seeking youths for depression, anxiety and substance use disorders, alcohol use disorders and a family history of substance use disorders were significantly associated with developing bipolar disorder, and depressive symptoms and cannabis use had further high effect sizes, despite not reaching statistical significance (Ratheesh et al., 2015).

The relevance of unspecific mental health symptoms has been demonstrated in a review of prospective cohort studies, investigating risk factors for the development of bipolar disorder: More than 50% of the individuals who developed bipolar disorder, experienced unspecific prodromal symptoms - even before the age of 14 years – similar to those preceding the onset of psychosis and depression (Geoffroy, Leboyer, & Scott, 2015). This finding supports the stage description of the clinical staging model, with early stages consisting of undifferentiated general symptoms and syndromes (Lin, Reniers, & Wood, 2013, see Section 1.3.2).

Brain imaging revealed significant volume reductions in the amygdala and insula in UHR for psychosis individuals who subsequently developed bipolar disorder, as compared to UHR for psychosis individuals who did not develop any psychiatric disorder at least 12 months after the scan, and healthy controls (HC) (Bechdolf et al., 2012). This gives preliminary evidence that imaging studies might help to predict who is subsequently going to transition to bipolar disorder (at least in symptomatically enriched clinical samples) (Bechdolf et al., 2012).

1.2.2 Psychosis

Schizophrenia is one of the most common psychotic disorders and debilitating in its nature, therefore extensive research has focused on its aetiology. Schizophrenia has a strong genetic component, is more prevalent in males and individuals with migration history, and further associated with urbanicity, cannabis use, prenatal infections, and perinatal complications (Tandon, Keshavan, & Nasrallah, 2008). Even though a number of genes and chromosomal abnormalities have been linked to an increased risk for developing schizophrenia, no single gene variation could be consistently identified (Tandon et al., 2008). Neurodevelopmental abnormalities were proposed to be the result of errors in synaptic pruning during adolescence and early adulthood (Shenton, Dickey, Frumin, & McCarley, 2001). Amongst brain abnormalities, such as ventricular enlargement, and involvement of the frontal and parietal lobe, and diverse subcortical structures, the temporal lobe has been viewed as the key to understanding the pathogenesis of schizophrenia due to its importance in language and memory processes (Shenton et al., 2001). The observation of insular activation during hallucinations suggests that the insula is creating heightened salience during otherwise normal activity, supporting the notion of an insular dysfunction model of psychosis (Palaniyappan & Liddle, 2012). The psychopathology of schizophrenia has further been attempted to be explained by anatomical and functional dysconnectivity (Stephan, Baldeweg, & Friston, 2006), and hypo-frontality (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Concepts of hypo-frontality and dysconnectivity in individuals with (sub-) threshold psychotic symptoms will be discussed in more detail in Section 5 and 6.

Ultra-high risk for psychosis

The period preceding the onset of schizophrenia and other psychotic disorders is characterised by non-specific symptoms such as anxiety and depressed mood, attenuated psychotic symptoms (e.g. delusions or hallucinations) and a decline in social and role functioning. To detect young people in the prodromal phase of psychotic illness, these characteristics have been operationalised and are known as UHR for psychosis (or clinical

high risk or the at-risk mental state). One way of defining these UHR criteria is by using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), and classifying into attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), and/or trait vulnerability.

For the APS criterion, symptoms must be present for at least once a week, with a frequency of at least several times per week. The BLIPS criterion refers to psychotic symptoms at the severity and frequency of a psychotic episode but which spontaneously resolve within 7 days. Trait vulnerability refers to young people with a first degree relative with psychotic illness, or schizotypal personality disorder in the individual, accompanied by a substantial deterioration in functioning, maintained for at least a month within the past year, or by chronic low functioning (Yung et al., 2005). Rates of transition to a first episode of psychosis (FEP) in individuals presenting with these features are estimated to be approximately 22% over twelve months, increasing to 29% after two years and 36% after three years according to a recent meta-analysis (Fusar-Poli et al., 2012), highlighting the importance of early intervention (McGorry et al., 2002) to reduce the risk of pronounced and possibly non-reversible structural brain alterations associated with progression to a first episode of psychosis (Wood, Yung, McGorry, & Pantelis, 2011). Special attention may need to be paid to the BLIPS group with highest rates of transition over the short term, followed by the APS group, and least risk of transition in the trait group (Nelson, Yuen, & Yung, 2011).

Neurobiological abnormalities in such individuals appear to be qualitatively similar but less severe than in schizophrenia (Jung, Borgwardt, Fusar-Poli, & Kwon, 2012). Region of interest (ROI) studies have identified smaller frontal (Mechelli et al., 2011), insular (Takahashi et al., 2009), parahippocampal (Mechelli et al., 2011; Tognin et al., 2014) and superior temporal gyri (Takahashi et al., 2010) volumes, characterising UHR individuals and/or predating the onset of psychosis, which has generally been replicated by whole-brain, voxel-wise brain morphometric studies (Fusar-Poli, Radua, McGuire, & Borgwardt, 2011). Progressively declining insular volumes were detected in UHR patients who subsequently transitioned to psychosis, when compared to those who did not transition and HC

(Takahashi et al., 2009), confirming the idea of an insular dysfunction model of psychosis (Palaniyappan & Liddle, 2012) even before the onset of psychosis. Such changes, which are also associated with the pathogenesis of schizophrenia, are assumed to be distributed, involving inter-connected brain networks rather than focal regions (Chen et al., 2014). This view is in accordance with the manifestation of abnormalities of brain networks in individuals at familial risk and UHR for psychosis: fMRI studies showed altered resting-state connectivity within the default-mode network (see Section 6.1) between the posterior cingulate cortex (PCC), precuneus, and prefrontal areas in individuals with a familial risk (Jang et al., 2011; Jukuri et al., 2013; van Buuren, Vink, & Kahn, 2012) and between diverse frontal and subcortical regions in UHR subjects (Dandash et al., 2014).

1.2.3 Anxiety disorders

Age of onset varies across anxiety disorders with separation anxiety disorder and some specific phobias having their onset before age 12, social phobia from later childhood to adolescence, panic disorder, agoraphobia, and generalised anxiety disorder (GAD) from adolescence to early adulthood (Beesdo, Knappe, & Pine, 2009). Estimates for lifetime prevalence for anxiety disorders in childhood and adolescence ranges from 15-20% (Beesdo et al., 2009). 12-months prevalence rates for social anxiety disorder, in particular, were about 2% and for sub-threshold social anxiety with one DSM criterion missing, 3%, and with two or more missing, 7.5% - all three groups being associated with greater impairment as seen in controls (Fehm, Beesdo, Jacobi, & Fiedler, 2008) and greater suicide risk (Balázs et al., 2013). Anxiety disorders are highly comorbid among each other and with other psychiatric disorders, and have a modest genetic predisposition in the range of 30-40% (Hettema, Neale, & Kendler, 2001). Amongst others are childhood adversities and life events, behavioural inhibition, and parental overprotection risk factors for developing anxiety disorders (Beesdo et al., 2009). Paediatric structural imaging reports inconsistent findings, e.g. some reporting increases and other decreases in amygdala volume (Pine, 2007).

Functional imaging studies discovered amygdala hypersensitivity - that is, increased

amygdala activation, e.g. when viewing emotional stimuli (Beesdo et al., 2009).

1.2.4 Eating disorders

Results from an adolescent national comorbidity survey revealed lifetime prevalence

of anorexia and bulimia nervosa, and binge-eating disorder being settled below 2%,

respectively; however, sub-threshold conditions of disordered eating are estimated to be

considerably higher (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011). Jacobi

et al. (2011) followed young women at increased risk for eating disorders due to high weight

and shape concerns, and found that 11% developed sub-threshold or full syndrome eating

disorders over a three year period. Especially those experiencing critical comments about

their eating behaviours and with a history of depression were at highest risk with a sensitivity

of 75% and specificity of 82% (Jacobi et al., 2011). In this survey, median age of onset was

quite consistently found to be around 12 years of age. Whereas anorexia nervosa was only

comorbid with oppositional defiant disorder (that is, a pattern of negativistic and hostile

behaviours that causes significant impairment in social and academic functioning; American

Psychiatric Association, 2000), bulimia nervosa and binge-eating disorder were strongly

associated with depressive and anxiety disorders. Disordered eating was further associated

with social impairment and suicidality. Even though the majority was seeking help for

emotional or behavioural problems, only a minority sought help specifically for eating

problems (Swanson et al., 2011).

A review about the neurobiology of eating disorders in children and adolescents

identified anorexia nervosa as often associated with obsessive and rigid personality,

perfectionism, and reduced affect, and bulimia nervosa with intense affect, high impulsivity,

and emotional dysregulation (Kaye, 2008). Genetic contribution to eating disorders was

estimated to be as high as 50-80%, with an often chronic and debilitating course of illness,

and high treatment resistance in anorexia nervosa. Neuroimaging studies detected

abnormalities in frontal, temporal, parietal, and cingulate brain areas (Kaye, 2008), similarly to other psychiatric disorders, e.g. as prefrontal and hippocampal abnormalities described in affective disorders (Thapar et al., 2012, see Section 1.2.1), and frontal, temporal, and parietal abnormalities in psychotic disorders (Shenton et al., 2001, see Section 1.2.2) .

1.2.5 Substance use disorders

High sensation seeking, low harm avoidance and impulse control, poor parenting skills, family conflict, lack of bonding, as well as substance disorders in first-degree relatives, and early behavioural problems have, amongst others, been identified as risk factors for developing substance use problems (Hawkins, Catalano, & Miller, 1992). Furthermore, physical and sexual abuse, as well as witnessing violence, increased the risk for substance use disorders (Kilpatrick et al., 2000), and males were more often affected (Hawkins et al., 1992).

Adolescent binge drinking and marijuana use has discrete, but significant effects on neurocognition, such as decreases in executive functions and attention, and memory impairment (Squeglia, Jacobus, & Tapert, 2009). These behavioural manifestations may be the consequence of grey matter reductions (e.g. of the hippocampus) in case of heavy drinking, and alterations in white matter (e.g. in frontal-occipital and superior longitudinal fasciculi, and in the splenium of the corpus callosum) and functional brain activation during cognitive tasks (e.g. activation increases in the parietal lobe and decreases in occipital and cerebellar areas during a spatial working memory task) for both, alcohol and cannabis (Squeglia et al., 2009).

1.2.6 Disorders' interrelations

Substance use in adolescence can be a coping strategy to deal with stress and associated negative emotions (Kilpatrick et al., 2000). Depressive (or other psychiatric) disorders often precede substance use disorders, which suggests the notion of self-

medication with alcohol or illegal drugs to cope with depressive symptoms; substances, in turn, can be seen as a *depressogens*, creating depressive feelings and neurovegetative symptoms of depression (Deykin, Levy, & Wells, 1987), ultimately leading to a vicious cycle of depression and substance abuse. Childhood trauma has been found to be significantly associated with becoming depressed and heavy drinking, and childhood trauma may worsen the association between recent life stress and depression (Colman et al., 2013).

The link between substance use and psychosis is further well established: Arseneault et al. (2002) demonstrated that 10% of adolescent cannabis users developed *schizophreniform disorder* in early adulthood, that is, symptoms of schizophrenia which do not reach the time criterion of 6 months to be diagnosed as schizophrenia. A dose-response relationship was discovered, with more increased risk for developing psychosis in those who consumed cannabis more frequently (Moore et al., 2007). The risk for developing psychosis is, however, not only elevated in individuals with frequent cannabis use, but in general when experiencing mental health problems: Recently, a large Danish nationwide registry study identified 25,000 individuals with child or adolescent psychiatric disorders, of which about 5% were subsequently diagnosed with schizophrenia spectrum disorders (Maibing et al., 2014). Comparing this number to the risk of developing schizophreniform disorder in the general population, it can be concluded that the risk is significantly increased in those individuals who experienced mental health problems in childhood or adolescence, according to this study, particularly within the first year, but also remaining significantly elevated for up to 5 years (Maibing et al., 2014).

When looking at longitudinal evidence, a large study is to be mentioned that identified sub-clinical psychotic symptoms at age 19/20 as risk factors for developing common mental disorders (e.g. dysthymia, social phobia, bipolar and obsessive-compulsive disorder) up to 30 years later (Rössler et al., 2011). A prospective cohort study following youth from age 12 to 18 found an association between psychotic symptoms at age 12 and depressive symptoms at 18, however, not the other way round (Sullivan et al., 2014). The authors explain these findings by the possible development of long-term trust issues, low self-

confidence and isolation due to experiencing psychotic symptoms in early adolescence; even if psychotic symptoms resolve, depressive symptoms might persist as consequence of these other mediating variables. The lack of association between depressive symptoms at age 12 and psychotic symptoms at age 18 is possibly due to the lack of such mediating variables that carry out long-term effects, as seen for psychotic symptoms (Sullivan et al., 2014). Another longitudinal study discovered adolescent substance use to follow externalising problems, and substance use in turn, being followed by criminal offences in males, and internalising problems in females may be preceded by substance use (Miettunen et al., 2014).

1.3 Approaches to mental health

The previous section outlined how mental disorders share risk factors, and aetiology, and how their psychopathology interacts over time with studies usually using a categorical approach based on classification systems of mental health. The use of categorical approaches to mental health has been well established, however, alternative approaches, such as viewing mental health on a continuum, have been proposed due to issues with the current classification systems. Therefore, after describing mental health from a categorical perspective and discussing issues that are associated with this approach (Section 1.3.1), alternative models dealing with these problems will be introduced. First, it will be described how mental health can be viewed on a continuum using a dimensional approach such as *clinical staging* (Section 1.3.2). Second, a *bifactor model* will be introduced which explains the psychopathology of mental disorders using a general underlying mental health factor (Section 1.3.3), and third, how using *nomothetic and idiographic parameters of mental states* can be used to facilitate intervention (Section 1.3.4). Lastly, issues that are associated with implementing these novel approaches into current diagnostic systems and clinical practice will be discussed (Section 1.3.5).

1.3.1 Categorical approach and issues associated with it

The DSM and ICD are the most commonly used manuals for diagnosis of psychiatric disorders in mental health research and clinical practice. The respectively latest versions are DSM-V (American Psychiatric Association, 2013) and ICD-10 (World Health Organisation, 1992) – both being numerous times revised, yet being classification systems since their first versions. Cloninger (1999) critically evaluated the principles underlying this categorical approach to mental health: Current classification systems underlie the assumption that mental health can be defined as the absence of mental disorder, with mental disorders being discrete, categorically defined entities. This categorisation aims to systematically and reliably describe cases, to serve as a model of disease aetiology and to effectively plan treatment. However, a substantial proportion of individuals present with intermediate or atypical cases, and are therefore classified as "not otherwise specified", or the replacement according to the DSM-V as "other specified" and "unspecified"(American Psychiatric Association, 2013). Drastically increasing the categories across DSM versions has, however, not solved that problem. Another point to mention is that the same medication or psychotherapy technique has often proven effective across different diagnostic categories. Early neuropsychiatric models assumed specific mental disorders would have their origin in specific areas of the brain, which has been overhauled by the contemporary notion of complex, distributed and interconnected neuronal networks (Cloninger, 1999, see Chapter 6).

Conventional diagnoses built on the DSM and ICD are delineated by contrived divisions based on symptom sets (McGorry et al., 2007). This approach is associated with three major issues. Due to the possibility of diverse symptom presentations within a particular disorder, a so-called within-category heterogeneity may result, which questions the validity of considering various symptom constellations to reflect the same diagnosis (Clark, 1995). A categorical approach further constitutes diagnoses as independently emerging conditions. Given the fact that they rather co-occur with other disorders, as e.g. a survey has demonstrated for major depression and panic disorder, it was found that patients with life-time comorbidity were generally more impaired and showed a more severe course than

those with one disorder alone (Roy-Byrne, 2000). Related to this is the question to whether

mental disorders are separated from one another by natural boundaries, which is found to

have little evidence and it is rather assumed that variation in symptoms follows a continuum

(Kendell & Jablensky, 2003). Impairment is more frequent in threshold diagnostic categories

than sub-threshold disorders, but due to the higher overall prevalence of the latter, recent

findings shift the attention away from diagnostic criteria and thresholds, towards impairment

and distress (for more information on functional impairment, see Section 1.4.3, Shah, 2015).

1.3.2 Dimensional approach and clinical staging

A dimensional approach, by contrast, hypothesises that mental disorders, such as

schizophrenia or affective disorders, develop from a *pluripotential* state, consisting of

undifferentiated general symptoms and syndromes and from a background of specific and

non-specific risk factors, such as genetic predispositions or early environmental and/or

traumatic conditions (Lin et al., 2013). Depending on individual characteristics like coping

responses, personality traits, social skills and further protective and risk factors as stated in

diathesis-stress-models (Ingram & Luxton, 2005), progression of symptoms and acquisition

of new symptoms might occur, which may be associated with progressive neurobiological

changes and behavioural and functional decline, until threshold disorders arise (Lin et al.,

2013). *Diathesis* is defined as predispositional sets of biological and psychological factors

that make an individual vulnerable to psychopathology. Whereas the term *stress* has been

conceptualised in many different ways, one could define stress as all major and minor life

events that interrupt an individuals' physiological, cognitive and emotional mechanisms to

maintain stability. This diathesis-stress-model suggests *additivity*, that is, whether or not a

mental disorder will develop, depends on the combined loading of stress and diathesis. E.g.,

minor stressors could be associated with disorder onset in an individual with a high genetic

loading, whereas only major life events would lead to disorder onset in an individual with low

vulnerability according to the model (Ingram & Luxton, 2005).

1.3.2.1 Clinical staging

One approach based on some dimensional principles in clinical practice is clinical staging. Clinical staging is a more concise form of diagnosis, which in contrast to conventional diagnostic practice, not only defines the extent of progression of an illness at a particular time point, but also where a person currently lies along the continuum of the course of the disease (McGorry et al., 2007). The aims are to delay or even prevent progression to more advanced stages or to remit to earlier ones (McGorry et al., 2007) and it allows for treatment selection relevant to stage, with a higher effectiveness in earlier stages through less invasive interventions than when delivered later in the illness course (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006). McGorry (2013) summarises that mental disorders are considered to be dynamic syndromes that overlap and share aetiologies and courses according to this model. Major psychiatric disorders are often preceded by *prodromes*, that is, sub-threshold stages (*microphenotypes*) consisting of non-specific symptoms, such as anxiety and depression, frequently being associated with persistent stress and disability. Access to care is typically only provided for threshold disorder, yet, the need for care often exists during the sub-threshold stages as well. This approach defines the stage by symptom severity, level of associated distress, and impairment of functioning, and persistence of problems in contrast to specification of syndromal content. The model acknowledges that persistent and multiple microphenotypes can justify clinical need in their own right, and on the grounds of risk for transition to frank disorder (*macrophenotypes*). It further acknowledges a "grey zone" between sub-threshold disorder and distress and more serious disorder, and aims to keep balance between over- and under-treatment (McGorry, 2013). Table 1.2 illustrates an example of the heuristic representation of a clinical staging model that defines stages from 0 to 4 on the basis of clinical symptomatology and the individuals' functioning. It further addresses which populations to target and which sort of intervention is likely to be indicated.

Table 1.2
Clinical staging framework for psychotic and severe mood disorders (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006)

Clinical stage	Definition	Target populations for recruitment	Potential interventions
0	Increased risk of psychotic or severe mood disorder No symptoms currently	1st degree teenage relatives of individuals with psychotic and severe mood disorders	Improved mental health literacy, family education, drug education, brief cognitive skills training
1a	Mild or non-specific symptoms of psychosis or severe mood disorder (including neurocog-nitive deficits) Mild functional change or decline	Screening of teenage populations, referral by primary care physicians, referral by school counselors	Formal mental health literacy, family psychoeducation, formal CBT, active substance abuse reduction
1b	Ultra high risk: moderate but sub-threshold symptoms, with moderate neurocognitive changes and functional decline to caseness	Referral by educational agencies, primary care physicians, emergency departments, welfare agencies	Family psychoeducation, formal CBT, active substance abuse reduction, atypical antipsychotic agents, antidepressant agents or mood stabilisers
2	First episode of psychotic or severe mood disorder Full threshold disorder with moderate-severe symptoms, neurocognitive deficits and functional decline	Referral by primary care physicians, emergency departments, welfare agencies, specialist care agencies, drug and alcohol services	Family psychoeducation, formal CBT, active substance abuse reduction, atypical antipsychotic agents for episode, antidepressant agents or mood stabilisers, vocational rehabilitation
3a	Incomplete remission from first episode	Primary and specialist care services	As for '2' with additional emphasis on medical and psychosocial strategies to achieve full remission
3b	Recurrence or relapse of psychotic or mood disorder which stabilises with treatment, residual symptoms, or neuro-cognition below the best level achieved following remission from first episode	Primary and specialist care services	As for '3a' with additional emphasis on relapse prevention and 'early warning signs' strategies
3c	Multiple relapses, provided worsening in clinical extent and impact of illness is objectively present	Specialist care services	As for '3b' with emphasis on long-term stabilisation
4	Severe, persistent or unremitting illness as judged on symptoms, neurocogntion and disability criteria	Specialised care services	As for '3c' but with emphasis on clozapine, other tertiary treatments, social participation despite ongoing disability

Notes. CBT=Cognitive-Behavioural Therapy.

Estimations of threshold DSM and sub-threshold disorder (anxiety, mood, attention deficit hyperactivity disorder, disruptive, and substance use disorders) from a probability sample of youths aged 11-17 years, revealed 12-months prevalence of 16% for threshold, and 42% for sub-threshold disorder when disregarding the impairment criterion (Roberts, Fisher, Blake Turner, & Tang, 2015). These numbers dropped to 8% and 16%, respectively, when considering impairment. 50% of threshold disorders were described by moderate to severe impairment, and 38% of sub-threshold disorders (Roberts et al., 2015). This higher prevalence of sub-threshold disorders compared to threshold disorders translates into significant illness burden of sub-threshold conditions on the population level (Shah, 2015). However, efforts to include those cases, e.g. into the DSM to provide access to clinical care, may pathologise these conditions to the level of threshold disorders, possibly leading to over-treatment and inappropriate medicalisation. Instead, clinical staging models and early intervention services could be reconfigured to include distressed and/or help-seeking individuals, regardless of diagnosis. This would decouple requiring to provide a diagnosis before treating individuals who are in need for clinical care and minimise the risk of overtreatment, by still aiming to prevent or delay transition to frank disorder (Shah, 2015).

1.3.2.2 Trunk and branches model

The *Trunk and Branches* model is a heuristic representation that has been adapted from the clinical staging model (McGorry et al., 2006; Purcell et al., 2015). Stage descriptions are very similar to the clinical staging model (as illustrated in Table 1.2), with the main difference being that additional branches are described from stage 2 onwards, covering not only psychotic and severe mental disorders, but also branches of anxiety, eating and substance use disorder. It proposes a stage 0, describing asymptomatic individuals, presenting with no or only very few depressive and anxiety symptoms. Stage 1a encompasses undifferentiated general symptoms (mild anxiety, depressive and somatic syndromes), whereas stage 1b describes individuals with an attenuated form of a

distinguishable disorder. Stage 2 describes threshold disorder (e.g. MD, mania, psychosis) (see Figure 1.1). Progression might take place, often accompanied by functional decline and development of chronic symptoms; however, transition from one stage to the next is not inevitable (Purcell et al., 2015), as well as remission of symptoms being likely to take place.
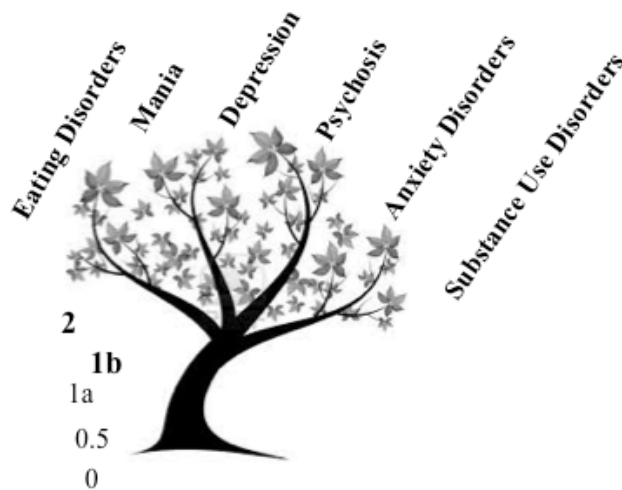
Figure 1.1. Trunk and Branches Model.

1.3.3 Bifactor model

It was aimed to distinct "normal" from "disordered" behaviour with the introduction of DSM-IV, to select a threshold above which the risks associated with labelling and treating mental problems would outweigh the risks associated with not labelling and treating these problems as a mental disorder (Lahey et al., 2008). However, over time accumulated evidence indicated that current diagnostic boundaries do not sufficiently regard child and adolescent psychopathology (Sonuga-Barke, 2013). Instead, using a differentiation into higher-order liability dimensions of internalising and externalising disorders may be more useful (Brodbeck et al., 2014). This liability-spectrum model proposes a *distress* factor including major depressive, dysthymic and generalised anxiety disorder, and a *fear* factor including social, specific and agoraphobia and panic disorder on the internalising dimension. Substance disorders count towards the externalising dimension (Krueger & Markon, 2006). Internalising disorders appear to be too highly correlated to show meaningful individual

contributions in classifying psychopathology in the early ages of childhood and adolescence (Lahey et al., 2008). High correlations between diagnoses such as MD and GAD were discovered, which seem likely to be reflected by symptoms shared between the two diagnostic categories such as insomnia, irritability, and difficulties to concentrate (Lahey et al., 2008). Abnormal sleep duration has repeatedly been shown to severely affect individuals' health, cognition and mood (Waters & Bucks, 2011). More recently, low prevalence disorders such as bipolar and eating disorders were found to form sub-factors within the internalising dimension (Forbush & Watson, 2013). It has furthermore to be acknowledged that with only looking at threshold mental disorders, cases of sub-threshold depression and anxiety are overseen, which were found to be related to functional impairment and suicidality in those adolescents (Balázs et al., 2013). Effect sizes for predicting future psychopathology of the internalising and externalising dimensions yielded small to moderate effect sizes (Patalay et al., 2015).
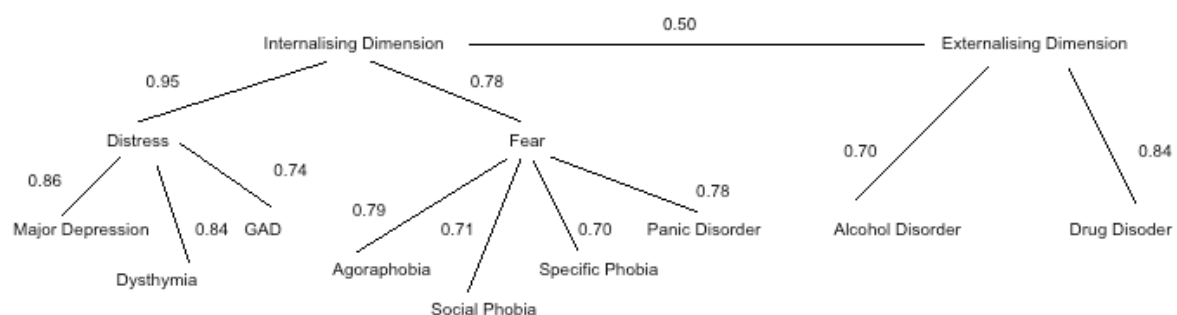
Figure 1.2. Path diagram of correlations of best-fitting DSM disorders with internalising and externalising dimensions (Krueger & Markon, 2006).

A so-called *bifactor* or *general-specific model* was shown to represent psychopathology better than categorical approaches (Brodbeck, Abbott, Goodyer, & Croudace, 2011), and better than internalising and externalising dimensions, predicting future psychopathology with large effect sizes and significantly predicting young people's functioning (e.g. academic attainment) (Patalay et al., 2015). The bifactor model proposes a general distress factor underlying depression and anxiety symptoms accounting for their

commonality and being a strong non-specific predictor for future anxiety and affective disorders, and further domain-specific factors accounting for the remaining variance. Unique information above the general distress component was revealed for the independent factors hopelessness-suicidal ideation, and generalised worrying in a study including 14-year old adolescents. These specific factors distinguished individual features of DSM disorders and also predicted future clinical diagnoses at age 17 (Brodbeck et al., 2014). A recent cross-sectional study which looked at a cohort of 13 and 18 years olds, supported the bifactor model, by demonstrating that depressive, anxiety and psychotic symptoms were best represented with a unitary common mental distress factor, on which psychotic symptoms constituted the more severe end of psychopathology (Stochl et al., 2015). Sleep disturbance may likely be associated with this common mental distress factor, as it either often constitutes a diagnosable symptom as seen in MD and GAD (American Psychiatric Association, 2000), or sleep disturbance frequently accompanies psychiatric disorders and likely affects their course, e.g. in schizophrenia and alcohol disorder (Krystal, Thakur, & Roth, 2008).

A further factor to consider for the extent of expression of depressive, anxiety and psychotic symptoms, are risk factors. The level of vulnerability for psychopathology varies according to the existence and interplay of two groups of risk processes – distal and proximal vulnerabilities. Distal vulnerabilities include genetic risk factors and childhood adversities (maltreatment, life events etc.) that influence prodromal dimensions of psychopathology in terms of mood, feelings and behaviour. Proximal vulnerabilities emerge later in time during adolescence and influence individuals' stress response, including variations in hormonal levels, such as of cortisol and dehydroepiandrosterone, the extent of cognitive control over one's emotions as well as the presence of psychiatric disorders (Goodyer, Croudace, Dunn, Herbert, & Jones, 2010).

1.3.4 Nomothetic and idiographic parameters of mental states

Wigman et al. (2013) suggested that mental disorders can be cut down to sets of symptoms that are linked through causal relations. A system that combines *nomothetic* and *idiographic* parameters of mental states, hypothesises that the strength and variability which connects these mental states, varies across different stages of psychopathology, that is, links between those mental states become stronger and more divergent over the course of time. Psychiatric diagnosis can be promoted by coupling a group-based classification (= nomothetic component, e.g. diagnostic categories) across early stages, and with progression of stages, by an individual-specific psychopathological profile (= idiographic component) (Wigman et al., 2013). This model assumes that whereas earlier stages demonstrate greater similarity in clinical expression, expression of these mental states increasingly varies across individuals in later stages.

When considering the heterogeneity of diagnostic classifications (see Section 1.3.1, e.g. with regards to symptom expression, need for clinical care, course of the illness, risk factors, response to treatment, and environmental context of an individual), it appears implausible that these labels can provide sufficient clinical utility (van Os, Delespaul, Wigman, Myin-Germeys, & Wichers, 2013). *Contextual precision diagnosis* is an idiographic means that can be used across all stages of psychopathology that facilitates a precise indexing of treatment needs and monitoring of treatment response. Momentary assessment technologies, such *Experience Sampling Method*, capture the dimensional variation of mental states and their interaction with each other and environmental variation, with the result of a contextual and precise diagnosis. These novel methods are considered to be an important addition to ordinary diagnostic classification in psychiatry (van Os et al., 2013).

Wigman et al. (2012) proposed (similarly to the theoretical assumptions of the bifactor model) that mental health symptoms are considered to fluctuate as a function of an underlying latent construct (that is, in the sense of a general mental health factor that underlies depressive, psychotic and anxiety symptoms) and that dimensions of psychopathological symptoms reciprocally affect each other over the course of time and

share risk factors. In this model, psychotic symptoms are included in addition to depression and anxiety symptoms. It has been suggested that some of the individuals at UHR for psychosis, in fact, present with depression or anxiety disorders which are complicated by sub-clinical psychotic symptoms (Wigman et al., 2012). This is supported by the finding that antidepressant treatment was highly effective for part of a UHR group (Cornblatt, Lencz, & Obuchowski, 2002). Likewise, neuroleptics have proven to be effective in treating anxiety and affective disorders, giving evidence that lack of specificity also appears in daily clinical practice (Weiser, van Os, & Davidson, 2005).

1.3.5   Issues associated with novel approaches

Youth mental health is a fairly new discipline (McGorry et al., 2014), and combining dimensional and categorical approaches (McGorry, 2013) would add to understanding the complexity of the psychopathology of mental disorders. However, before implementing new models of youth mental health in order to facilitate early intervention, evidence for their validity is needed (McGorry et al., 2014); giving evidence for better health outcomes and economical benefits with this proposed mental health reform is difficult to achieve, given the long-term nature of validating mental health outcomes. Yet, the implementation of novel youth mental health models which have evolved in the past 10 years, is encouraged by evidence-based staging and early intervention in psychosis (McGorry et al., 2014).

Hickie et al. (2013) applied a clinical staging model to a cohort of young help-seeking people with depressive, anxiety, and psychotic symptoms and impairment in role function. Even though reliable clinical stage ratings were derived from patient records (Hickie et al., 2013), staging was implemented without explicit landmarks and cut-offs for the employed psychometric measures. Clinical staging models overlap in their essence, however, stages are often slightly differently defined. E.g. Hickie et al. (2013) and McGorry et al. (2006) used impairment in functioning as criterion for stage definition, whereas others do not include functioning as criterion, but rather solely define it with clinical symptomatology (Purcell et al.,

2015). These inconsistencies, together with a variety of other proposed dimensional approaches to mental ill health, complicate the application and integration of these novel ideas into clinical practice, and the translation into classification systems such as the DSM and ICD.

1.4 Improvement of prediction of clinical outcome

Various research groups have spent the last two decades aiming to identify individuals at heightened risk for developing a psychotic disorder and to provide rationales for early intervention to prevent transition. Amongst those are the Australian group of the Personal Assessment and Crisis Evaluation (PACE) clinic, the European Prediction of Psychosis Study and the North American Prodrome Longitudinal Study group. The disability that is accompanied by psychotic illness develops long before its onset - that is why staged treatment was considered to be effective during the prodromal phase of psychosis by ameliorating, delaying or possibly even preventing frank disorder (McGorry et al., 2009). Despite the UHR state being a valid construct and having proven to be consistently associated with an increased risk of transitioning to psychosis (Fusar-Poli et al., 2012), the prospective identification of this prodromal phase is challenged by the non-specific nature of symptoms occurring (Yung, Phillips, & McGorry, 2004). There is a considerable overlap in psychiatric symptoms preceding the onset of schizophrenia and psychopathological experiences in the general population (Koutsouleris et al., 2009), as well as symptoms preceding the onset of other mental illnesses, e.g. depression or anxiety disorders (Lin et al., 2013). Single prodromal symptoms are only to a limited extent useful as diagnostic markers for predicting outcomes on the individual level (Koutsouleris et al., 2009).

Section 1.4.1 describes how predictive accuracy of the UHR state for psychosis (as the best worked example of clinical staging in psychiatry) can be improved as the first step. The second step is to refine treatment by selecting treatments relevant to stage (Section 1.4.2) in psychosis and other psychiatric disorders. Section 1.4.3 briefly refers to the importance of

improving functional (and not only clinical) outcome, and encompasses the relevance of monitoring non-psychotic outcomes in individuals at UHR for psychosis.

1.4.1 Improvement of accuracy for the prediction of transition from UHR to FEP

Various attempts have been undertaken to improve the predictive accuracy of the UHR state. For example, a family history of schizophrenia together with functional decline, high levels of unusual thought content and paranoia, social impairment and substance abuse were found to uniquely contribute to the prediction of psychosis in at-risk individuals with positive predictive powers ranging from 43-52% as compared standard criteria (Cannon et al., 2008). High levels of negative symptoms, such as emotional and cognitive disturbances and low energy, predicted psychosis better than sub-threshold positive symptoms; whereas negative symptoms predicted transition with a an estimated hazard ratio of 1.83, was the estimated hazard ratio for positive symptoms only 1.28 (Yung et al., 2005). Machine learning algorithms, such as multivariate neuroanatomical pattern recognition (including structural magnetic resonance imaging (MRI) data, looking at volumetric changes over time in order to predict transition) further facilitated early detection and disease prediction of the UHR state in psychosis on the individual level: support-vector regression revealed reliable prediction of longitudinal brain changes between those individuals who transitioned and those who did not with a normalised root mean square deviation of 26% (Koutsouleris et al., 2009).

1.4.2 Staged treatment

More than half of UHR individuals will not transition to psychosis in the medium term considering estimates of transition rates of 36% within 3 years (see Section 1.2.2). However, clinical interventions during the UHR state do not have the sole purpose to prevent or delay transition, but also to manage and improve actual symptom presentation, which is often more a concern from the patient's perspective than the actual risk of transition (Fusar-Poli et

al., 2012). McGorry et al. proposed to aim for phase-specific treatment: This means refining treatment by employing a sequential approach, with safer treatments in the early stages of mental illness (e.g. during the UHR state) according to the clinical staging model, and more intense treatment with non-improvement. One example of an early and safe treatment are omega-3 fatty acids which were found to be effective in UHR individuals in reducing positive and negative psychotic symptoms and improving functioning. However, those were not found to be effective in chronic schizophrenia. Apart from neuroleptics, antidepressants and cognitive(-behavioural) therapy have been found to be effective in reducing transitions, and generally reducing psychiatric symptoms over the follow-up period. The choice of treatment underlies risk-benefit considerations depending on the individual's clinical stage of illness (McGorry et al., 2006; McGorry et al., 2009).

Longitudinal studies show that adolescent sub-syndromal depression increases the risk of transition to threshold depressive disorder, and that depression during adolescence predicts anxiety, substance use, and bipolar disorder, as well as suicidal behaviour, unemployment and general health problems (Thapar et al., 2012). Insomnia can be seen as a further independent risk factor: Non-depressed individuals with insomnia were found to be at two-fold risk for developing depression as compared to individuals with healthy sleep patterns (Baglioni et al., 2011). Early outreach and intervention is therefore not only important in UHR individuals but also in other psychiatric disorders: If depressive episodes can be detected and treated before such subsequent secondary adverse consequences emerge, further episodes could be prevented (Kessler et al., 2001). Furthermore, if risk factors for substance abuse can be reliably identified (see Section 1.2.5), a risk-focused approach can be employed to prevent substance use problems in adolescents and young adults (Hawkins et al., 1992). Similar effects can be found in eating and anxiety disorders: Early recognition of disordered eating can prevent transition to frank eating disorder (Rome et al., 2003), and early intervention in anxiety disorders in children and youths has led to maintenance of outcome improvement and reduced substance involvement or other

associated problems years after therapy (Kendall, Safford, Flannery-Schroeder, & Webb, 2004).

1.4.3 Prediction of nonpsychotic disorders and association with functional outcome

It is further crucial to determine whether UHR criteria not only detect people at risk for developing psychosis but also for non-psychotic disorders (Fusar-Poli et al., 2013): Psychotic experiences were commonly found to be associated with other psychopathology, such as depressive and anxiety disorders (Lin et al., 2015). Addington et al. (2011) investigated clinical and functional outcome of so-called false-positives (or non-transitioning individuals), and revealed that 50% of this non-transition sub-group no longer displayed any (sub-threshold) psychotic symptoms after 2 ½ years of follow-up. Even though this group significantly improved in functioning, functioning was still lower than in a non-psychiatric control group, indicating that the UHR state is associated with persistent disability, at least in the medium term. Initially, at baseline, 53% of UHR individuals who did not transition had comorbid anxiety, 35% depression, 1% mania, and 11% substance use disorder. These numbers dropped after 2 years to 32% anxiety, 14% depression, 1% mania, and 4% substance abuse disorders. With approximately 35% of the sample developing a psychotic illness (Addington et al., 2011), it can be concluded that the UHR state predicts considerable psychopathology in about two thirds of the sample in the medium term. The finding of about two thirds of UHR individuals presenting with some sort of mental disorder was replicated by Lin et al. (2015). Within a follow-up period of up to 14 years, a very high percentage of these two thirds presented not only with one, but rather at least another psychiatric disorder. Therefore, UHR criteria may also represent a useful system for the identification of young people going to develop nonpsychotic disorders (Lin et al., 2015).

Scott et al. (2014) looked at a large sample of young people with affective disorders who were seeking help at clinical services for the first time. Individuals presented with at least one comorbid disorder in half, and with polysubstance use in one third of the cases.

Comorbid anxiety and daily cannabis and/or nicotine use were significantly associated with impaired functioning. This association of comorbidity and substance use with disability (which has been observed in a similar pattern in older adult samples) indicates that more outcome measures should focus on functional instead of symptom-specific measures (Scott et al., 2014).

1.5 Structure of the thesis

After generally describing the sample, recruitment, and interview and self-report measures in Chapter 2 (General Methodology), four empirical chapters are introduced. Each of those chapters is divided into the sections introduction, methods, results, and discussion. Chapter 3 only encompasses individuals presenting at clinical services with early mental health problems, whereas chapters 4-6 compare a subset of this clinical sample with a group of HC. Only individuals with either a family history of mental disorders and/or whose mental problems subjectively did not improve after 6 weeks, were considered for this sub-group, in order to enrich the sample in terms of likelihood of transitioning from sub-threshold to threshold disorders, according to the proposed staging model.

Chapter 3 is a clinical chapter, which describes associations of depressive, psychotic and anxiety symptoms, and social and role functioning from baseline assessment until 6 months after. Associations of symptom sets are examined on a continuum, respectively, but also by categorising into individuals who are at UHR for psychosis. The role of social and occupational functioning is critically discussed for this categorisation, as well as an outcome measure.

Chapter 4 looks at longer-term stress levels associated with early mental health problems. Stress levels are objectively investigated by means of hair cortisol analyses, as well as subjectively via self-report. These measures are chosen to evaluate whether distress is present in the early stages of mental health problems and how cortisol is associated with clinical symptoms and functioning.

Chapter 5 illustrates functional neuroimaging findings during a working memory task. Individuals with mental health problems are compared with HC concerning task performance and differences in brain activation. Clinical participants with high and low symptom and functioning scores are furthermore compared with the respectively other group, and HC, and cortisol levels (as reported in Chapter 4) are included in analyses of covariance (ANCOVA).

Chapter 6 comprises another fMRI study, similar to study 5, however, instead of including a task, brain activation is observed during rest. Independent component analyses (ICA) are employed, and independent components are estimated using a single group ICA, and dual regression is used to create individual spatial maps of networks, which are compared between groups using permutation tests.

Chapter 7 summarises main findings and discusses these clinical and neurobiological correlates, aiming to integrate them into the early stages of a clinical staging model. Implications for clinical practice and future research are reviewed, followed by a conclusion.

CHAPTER TWO

GENERAL METHODOLOGY

This chapter briefly describes the employed research design (Section 2.1), followed by a description of participants of the clinical and control group (Section 2.2). The procedure underlying this thesis will be explained (Section 2.3), as well as a detailed description of employed measures be given, which are relevant for the majority of empirical chapters (Section 2.4). Lastly, it is highlighted how the classification into UHR for psychosis and psychotic-like experiences (PLE) is conducted (Section 2.5).

2.1 Research design

This thesis used data collected from a cohort study of help-seeking youths with early mental health problems. These youths were assessed via interview and self-report at baseline, after 3, and 6 months. As outlined in Section 1.5, only those individuals were considered for the neurobiological subgroup analyses in Chapters 4-6, who either had a first-degree family history of mental disorders and/or whose mental problems did not improve subjectively 6 weeks after the baseline assessment.

Neurobiological assessments were arranged upon MRI scanner and individual availability, and considering scanning safety issues (e.g. allowing for an appropriate gap between acquisition of new tattoos, piercings, and scan), ranging from 0-199 days after the clinical baseline assessment. A timeline of the research design is illustrated in Figure 2.1.
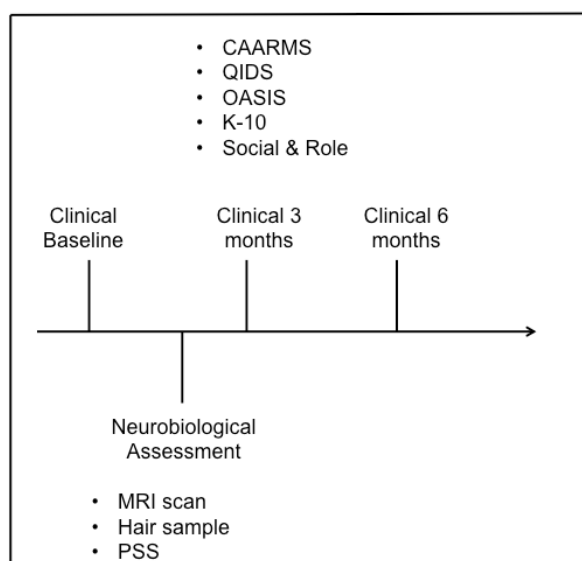
Figure 2.1. Timeline of research design.

2.2 Participants

73 clinical participants who were experiencing psychological distress participated in the main study. Clinical participants were recruited from the South Birmingham area via services specialised in (youth) mental health (Youthspace & Birmingham Healthy Minds) and via local advertisements. Inclusion criteria were the ages between 16-25 years, and help-seeking for mental health problems at entry to the research programme, however, none of the clinical participants had a diagnosed first episode of psychosis or primarily presented with psychotic symptoms. Exclusion criteria were a lack of sufficient English and cognitive ability to provide informed consent and adequately complete the assessments.

Youthspace is a youth-focused secondary mental health service that provides support for 16-25 years olds with mental health problems. The service sees young people with a variety of diagnoses and has no specific exclusion criteria. Youthspace offers a variety of treatments and case management provided by a multi-disciplinary team. Birmingham Healthy Minds is a primary care psychological therapies service, offering brief psychological talking therapy for individuals aged 16 and above who present with depressive and anxiety

symptoms. Their exclusion criteria are bipolar disorder, psychosis, suicidality or in need of long-term care. Both services operated primarily though GP referral at the time of study recruitment.

2.3 Procedure

The study was approved by the local ethics committee and baseline recruitment commenced in August 2012, and ended in August 2013. Individuals were followed up after 3 and 6 months. Clinical participants were either approached by researchers or clinical staff at the early intervention services, and pre-consent to be contacted was collected, or clinical participants responded to local advertisements at these facilities and contacted the research team themselves. Figure 2.2 illustrates the recruitment and assessment of clinical participants via a STROBE diagram (according to recommendations from von Elm et al., 2007) - that is, how the clinical sample was achieved. This diagram gives an idea of (1) how many individuals were examined for eligibility, (2) were confirmed eligible, (3) were included in the study at baseline and how many have completed the follow-up assessments at (4a) 3 and (4b) 6 months. The starting point of a STROBE diagram would usually estimate - in this case, how many clinical participants were potentially eligible. However, despite attempts to track this number with the clinical services, no estimation could be attained to date. Furthermore, 7 individuals were recruited via poster advertisements. Recruitment via posters makes it further difficult to make an estimation for those eligible, since services where posters were presented, shared facilities (e.g. with GP practices), and individuals who were not primarily attending meetings with Youthspace and Birmingham Healthy Minds, may have been eligible to partake in the study. This means a large pool of individuals may have potentially been eligible due to their help-seeking behavior for mental health problems.
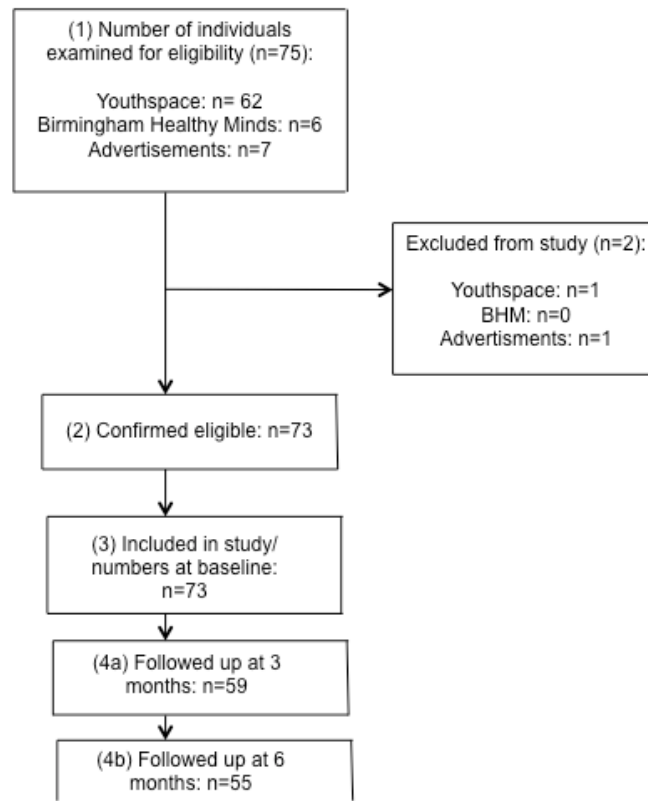
Figure 2.2 STROBE diagram (according to recommendations from von Elm et al., 2007).

The nature of the study was discussed via telephone and if individuals were interested, assessments were conducted at the University of Birmingham or participants' homes (or in rare cases for follow-up assessments conducted via telephone). For clinical participants aged 18 and above, informed consent was collected from them, and for clinical participants aged 16-17 years, additional parental consent was acquired. Assessments comprised of an interview and self-report and were conducted on a one-to-one basis by a member of the research team. All members of the research team were trained in the use of each measure. Each assessment generally lasted 1-2 hours and participants were reimbursed with £20.

2.4 Measures

Demographic information covered participants' age, gender, ethnicity, occupation and highest qualification, relationship status and whether having children. Individuals were assessed for psychotic, depressive, anxiety symptoms and social and role functioning via interview and self-report. These measures are described in the following sections, as they are relevant for most empirical chapters. Information on other measures (e.g. for the brain imaging and hair cortisol analyses, or chapter-specific interview and self-report data) is described in the respective empirical chapters.

2.4.1 Comprehensive Assessment of At-Risk Mental States (CAARMS)

The CAARMS is a semi-structured interview, designed to determine if individuals meet criteria for being at UHR for psychosis and it includes a threshold beyond which psychosis is assumed. It is a dimensional instrument to quantify severity (0 = absent/never, 6 = psychotic and severe) and frequency of psychotic symptoms (0 = absent/never, 6 = continuous) on a 7-point scale (Yung et al., 2005). The positive symptoms dimension of the CAARMS was administered, comprising of the four sub-scales: Unusual Thought Content (e.g. delusional mood, overvalued ideas), Non-Bizarre Ideas (e.g. suspiciousness, grandiosity), Perceptual Abnormalities (e.g. distortions, illusions, hallucinations), Disorganised Speech (e.g. difficulties with speech and communication). A combination of intensity and frequency ratings allows for the determination if individuals meet criteria for being at UHR for onset of a FEP or to indicate the development of a FEP. A score of at least 3 for both intensity and frequency on at least one sub-scale indicates UHR status, if coupled with a decline in functioning or chronic low functioning. Criteria for psychosis are met if clinical participants score a 6 on intensity and at least a 4 for frequency on non-bizarre ideas, unusual thought content and disorganised speech or a 5-6 on intensity and a 4-6 on frequency for perceptual abnormalities. Good to excellent agreement for intra-class correlation coefficients were reported for CAARMS sub-scales with an overall score for inter-rater reliability of 0.85. CAARMS criteria displayed good concurrent (e.g. with the Brief

Psychotic Rating Scale) and predictive validity (e.g. higher risk of transition to psychosis in individuals with an at-risk mental state) (Yung et al., 2005). For dimensional subsequent analyses, an index based on the sum of intensities and frequencies for the four sub-scales was calculated.

2.4.2 Social and Occupational Functioning Assessment Scale (SOFAS)

The SOFAS has been derived from the *Global Assessment Scale* (Endicott, Spitzer, Fleiss, & Cohen, 1976), giving a rating of overall psychological functioning on a scale from 0 to 100 (Goldman, Skodol, & Lave, 1992). The SOFAS is usually used to rate an individual's current functioning, however highest and lowest functioning ratings for the past 12 months have been employed additionally for the purpose of this thesis to determine a drop in functioning. Social and occupational functioning is considered on a continuum from excellent functioning to severely impaired functioning, however, this scale was only used for the purpose of determining UHR status.

2.4.3 Quick Inventory of Depressive Symptoms (QIDS)

The QIDS is a clinician-rated 16-item, semi-structured clinical interview to gauge severity of depressive symptoms over the past 7 days. Responses to the individual items are converted into the 9 DSM-IV symptom criterion domains (American Psychiatric Association, 2000), e.g. depressed mood, diminished interest, concentration problems. Each symptom item is scored on a 0 - 3 scale with total scores ranging from 0 – 27 allowing for a continuous approach to evaluate depressive symptomatology (Rush et al., 2003). QIDS scores can be classified into *none* (0-5), *mild* (6-10), *moderate* (11-15), *severe* (16-20) and *very severe* (21-27) depressive symptoms. A meta-analysis demonstrated acceptable psychometric properties with internal consistencies ranging from 0.65 – 0.87 (Chronbach's α) and concurrent validity, e.g. with the Hamilton Rating Scale for Depression, ranging from 0.72 - 0.79 (Reilly, MacGillivray, Reid, & Cameron, 2015).

2.4.4 Kessler Psychological Distress Scale (K-10)

The K-10 is a 10-item questionnaire, assessing general psychological distress by asking about depressive and anxiety symptoms in the past 30 days. Items prompt individuals to answer about how often they felt nervous, anxious, hopeless etc. on a 5-point scale ranging from "none of the time" to "all of the time", with scores ranging from 10 to 50. A total score ranging from 10-19 indicates the individual is likely to be well, 20-24, likely to have a mild mental disorder, 25-29, likely to have a moderate mental disorder, and 30-50, to be likely to have a severe mental disorder (Kessler et al., 2002). The K-10 is a moderately reliable instrument (kappa ($\varkappa$) ranging from 0.42 - 0.74) (Dal Grande, Taylor, & Wilson, 2002) and demonstrates good concurrent validity with other mental health instruments such as the General Health Questionnaire and current diagnosis of anxiety and affective disorders (Andrews & Slade, 2001).

2.4.5 Overall Anxiety Severity and Impairment Scale (OASIS)

The OASIS is a brief questionnaire to assess severity and impairment across multiple anxiety disorders and sub-threshold anxiety. Scoring of this continuous 5-item measure follows ratings from 0 (*none*), 1 (*mild*), 2 (*moderate*), 3 (*severe*) to 4 (*extreme)*, capturing frequency and intensity of anxiety, avoidance behaviour and interference of anxiety with everyday life and relationships, adding up to total scores ranging from 0 – 20, with a total score of 8 or above indicating an anxiety diagnosis (Campbell-Sills et al., 2009). The OASIS showed convergence with major anxiety measures (e.g. for social, post-traumatic stress, and generalised anxiety), a Chronbach's α of 0.84 for the five items (Campbell-Sills et al., 2009), and one-month re-test reliability of 0.82 (Norman, Hami Cissell, Means-Christensen, & Stein, 2006).

2.4.6 Global Functioning: Social and Role

The Global Functioning: Social (Auther, Smith, & Cornblatt, 2006) and Role (Niendam, Bearden, Johnson, & Cannon, 2006) scale provides clinician-rated, separate overall scores on scales from 1 – 10 for current, highest and lowest functioning in the past 12 months, with 10 indicating a superior functioning and 1 an extreme dysfunction. The Social scale evaluates peer relationships and conflict, age-appropriate intimate relationships and interaction with family members. The Role scale assesses performance in either school or other educational settings, work or as a homemaker. Inter-rater reliability for social and role functioning ranged from 0.85 – 0.95, and the social functioning scale was significantly correlated with social contacts (r = 0.70) and role functioning with work and school functioning (r = 0.57), demonstrating construct validity (Cornblatt et al., 2007).

2.5 Classification of UHR for psychosis, PLE and FEP

UHR criteria were defined using the CAARMS (Yung et al., 2005), comprising APS and BLIPS. For the APS criterion, symptoms must be present for at least once a week, with a frequency of at least several times per week. BLIPS refer to psychotic symptoms at the severity and frequency of a psychotic episode but spontaneously resolve within 7 days (see Section 1.2.2). UHR status was only given if individuals also displayed a 30% drop in functioning in the past 12 months or persistent low functioning (score ~ 50), as gauged by the SOFAS scale (Goldman et al., 1992). Individuals were referred to as PLE if they experienced APS or BLIPS (that is, UHR individuals) without a drop in functioning or chronic low functioning. A FEP was defined as at least one fully positive symptom several times a week for more than one week, that is, the first time when an individual experiences threshold psychotic symptoms.

CHAPTER THREE

THE ASSOCIATION BETWEEN POSITIVE PSYCHOTIC SYMPTOMS WITH DEPRESSIVE AND ANXIETY SYMPTOMS AND FUNCTIONING

Attenuated psychotic, depressive and anxiety symptoms constitute common features of emerging mental disorders in young people. These symptoms will subside either spontaneously or via early intervention for the majority of clinical participants. For a subset of clinical participants, however, symptomatology will progress, exerting a major impact on individuals' well-being, social and role functioning. 73 clinical participants presenting with mental health issues ($M_{age} \pm SD = 20.6 \pm 2.6$, range 16-26 years, 51 females) were assessed for psychotic, depressive, anxiety symptoms and social and role functioning via interview and self-report. These individuals were followed up with the same assessment battery after 3 (n = 59) and 6 months (n = 55). Clinical measures and functioning were longitudinally investigated, the association between symptoms determined, as well as predictors for future symptomatology and functioning identified. Clinical participants were classified into being at UHR for psychosis, experiencing psychotic(-like) symptoms, and no significant psychotic symptoms. No differences were found between UHR clinical participants and those with only psychotic-like experiences and no significant psychotic symptoms for the severity of depressive or anxiety symptoms, or functioning. Psychotic symptoms at baseline partly predicted social and role functioning and psychotic and depressive symptoms at 6 months. Overall, the whole population improved after 6 months. Psychotic-(like) symptoms in help-seeking young people appear to be associated with more severe depressive symptoms and poorer functioning, independent of UHR status, however, a robust predictive effect of psychotic symptoms in a general help-seeking population could not be confirmed. Neurodevelopmental trajectories of these associations with illness progression and transition to psychosis and other psychiatric disorders require wider longitudinal exploration.

3.1 Introduction

The major health problem in young people is mental health. While many individuals in this age group have transient illness, some persist into adulthood and can severely impair psychosocial functioning. Determining who will have these chronic problems can be difficult, especially in the early stages of disorder. Adolescents and young adults often present with unspecific symptoms and syndromes (Lin et al., 2013) such as depressive and anxiety symptoms, as well as PLE in these early stages.

PLE (*or* subclinical psychotic symptoms) are a milder form of clinical psychotic symptoms, which present with a lower intensity, frequency and level of associated distress (Yung et al., 2007). Nonetheless, PLE have been found to be associated with adverse outcomes in individuals at UHR for developing psychosis (Yung et al., 2003) and are also prevalent in other, non-psychotic psychiatric illnesses (Wigman et al., 2012). In UHR individuals PLE are associated with onset of psychotic disorders (Yung et al., 2003), with low psychosocial functioning and with the experience of comorbid psychiatric disorders such as MD (Rosen, Miller, D'Andrea, McGlashan, & Woods, 2006; Yung et al., 2007). With PLEs fluctuating against a background of non-psychotic psychiatric symptoms, this confuses the distinction between UHR and non-UHR patient populations (Yung et al., 2007). Situational anxiety, nervous tension and depression are, apart from actual PLE (such as hallucinations), additional risk factors for developing a psychotic disorder in genetic high-risk individuals (Owens, Miller, Lawrie, & Johnstone, 2005).

PLE are not only associated with psychotic disorders, but are also prevalent in depressive and anxiety disorders (Varghese et al., 2011). It has been hypothesised that PLE are not only a specific risk factor for developing psychosis, but rather a general, underlying predisposition to a range of mental disorders such as dysthymia, bipolar and obsessive-compulsive disorders, and social phobia (Rössler et al., 2011). In fact, they were found to be a risk factor for severe psychopathology, characterised by high comorbidity and suicidal behaviour (Kelleher et al., 2012b; Kelleher et al., 2012c). The joint presence of PLE in

depressive and anxiety disorders is common and therefore aetiologically relevant, as these mental states may reciprocally impact on each other (Wigman et al., 2012). As emotional problems often occur prior to or accompany psychosis, it has been inferred that an emotional involvement contributes to the development of positive psychotic symptoms (Freeman & Garety, 2003). However, since empirical evidence does not support a sharp differentiation between psychotic and affective disorders, it has been concluded that they rather share common maintenance processes (Freeman & Garety, 2003). Further support for this notion of broad endo-phenotypes arises from the fact that many risk factors, such as genetic disposition, trauma, and life events, are shared between psychiatric illnesses (Weiser et al., 2005). 57% of 11-13 and 79% of 13-16 year olds who experienced psychotic symptoms had a lifetime diagnosis of at least one non-psychotic psychiatric disorder, indicating an increasing predictive power of general psychopathology with increasing age from early to mid-adolescence (Kelleher et al., 2012b).

A meta-analysis of population-based studies found that some sort of psychotic symptoms occur in about 7.5% of 13 to 18 year olds, with a general decline from childhood to adolescence (Kelleher et al., 2012a). Psychotic symptoms during childhood predict increased rates of psychotic symptoms in adulthood (Poulton et al., 2000; Welham et al., 2009), and persisting psychotic symptoms were found to be associated with a greater risk for transition to a FEP in a dose-response fashion (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011). A psychosis-proneness persistence model suggests a possible synergism between environmental factors (such as trauma, cannabis use, and urbanicity) and psychotic symptoms, in predicting the subgroup that will present with persistent psychotic symptoms (Cougnard et al., 2007) and eventually transition to threshold disorder. Given that these risk factors occur only in a subset of individuals with psychotic symptoms, this may explain why most developmental expression of psychotic symptoms remains transient.

The prediction of psychosis still comprises substantial uncertainty despite diverse attempts to increase sensitivity and specificity (Ruhrmann, Schultze-Lutter, & Klosterkotter,

2010). The criterion of 30% decline in functioning or chronic low functioning has been added to the UHR criteria that are using the CAARMS (Yung et al., 2008). However, the European Prediction of Psychosis study identified a substantial loss of sensitivity in transitions, when this drop in functioning was incorporated. Except for the purpose of an enrichment strategy that theoretically predicts transition, the inclusion of this drop in functioning may be too restrictive (S. Ruhrmann, personal communication, 11 June 2014). Therefore, in this study, both options - with and without drop in functioning were considered when looking at clinical and functional outcome.

Recent studies for transition rates from UHR status to a FEP are estimated to be 22% within 12 months (Fusar-Poli, 2012) and 3-year persistence rates of psychotic symptoms in two general population samples were as high as 26-31% (Cougnard et al., 2007). Even though mental health symptoms (including psychotic symptoms) are transient for the majority of children and adolescents (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), there is a need for specialist mental health services, for those whose problems do not resolve on their own (Wang, Sherrill, & Vitiello, 2007). Early intervention in psychosis was found to yield better clinical and functional outcomes (Killackey & Yung, 2007) and significantly reduced incidence rates in at-risk adolescents (Clarke et al., 1995), and significantly reduced symptom scores in adolescents with depressive disorders (March et al., 2004). Further, interventions in depressed adolescents, such as interpersonal psychotherapy, were found to improve social-interpersonal functioning (Mufson, Weissman, Moreau, & Garfinkel, 1999).

A recent study by Hickie et al. (2013) employed a clinical staging model of mental disorders to help-seeking young people, with the majority being assigned to the early stages of mental health problems, which has been designed in a similar fashion to the current study. Even though individuals may not meet specific criteria for frank disorders, the early phases of mental illnesses are often symptomatic and associated with functional impairment and disability. Participants in this study accessed specialised treatment, however, up to one third

of individuals progressed to more advanced stages, with the highest risk of transition being within the first 12 months after presentation (Hickie et al., 2013). 38% of this cohort were experiencing sub-threshold psychotic symptoms and a further 7% symptoms classified as frank psychotic. 22% were experiencing no, 32% mild, 28% moderate, 14% severe and 4% very severe depressive symptoms at baseline (Purcell et al., 2014).

A neurodevelopmental model, e.g. of schizophrenia, proposes impaired academic and social functioning during adolescence as signs of a biological vulnerability to schizophrenia (Cornblatt et al., 2007; Cornblatt et al., 2003) and therefore targets of early intervention. On the other hand, more than half of the patients treated for schizophrenia in adolescence displayed educational, occupational and social dysfunction 10 years after their first episode (Lay, 2001), illustrating how psychotic symptoms impact on functioning, and vice versa. This association between functioning and clinical symptoms has also been demonstrated in other mental health issues: High social functioning, in terms of belonging to a high-status crowd, positive qualities in friendships and presence of a dating relationship protected against feeling socially anxious, whereas peer victimisation and negative interactions in friendships predicted high social anxiety and depressive symptoms (La Greca & Harrison, 2005). Experiencing a depressive episode during adolescence predicted impaired psychosocial, interpersonal and occupational functioning in young adulthood (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003) and educational underachievement and unemployment later in adolescence and early adulthood (Fergusson & Woodward, 2002). Patients with non-psychotic psychiatric disorders but additional psychotic symptoms showed lower global functioning than those without psychotic symptoms, potentially moderated by poor coping strategies such as avoidance-oriented coping (Wigman et al., 2014), implicating an additive effect of specifically psychotic symptoms over depressive and anxiety symptoms. Overall, this gives evidence that social and role functioning and clinical symptoms are mutually impacting on each other.

Psychotic symptoms appear to be especially important, posing a specific risk factor for developing psychosis. This is further supported by UHR criteria significantly predicting the onset of psychotic disorders (Yung et al., 2008). However, psychotic symptoms are a risk factor for a range of other mental disorders as well (Rössler et al., 2011). Therefore, the aim of this study was to determine whether UHR and non-UHR patient populations actually differ concerning clinical measures, such as depressive and anxiety symptoms, and functioning, to ultimately infer how psychotic symptoms are related to other clinical outcomes. Secondly, the general course of (sub)clinical psychotic and depressive symptoms and functioning was monitored and the association between (sub)clinical psychotic, depressive and anxiety symptoms and functioning was longitudinally investigated. It was hypothesised that clinical measures and functioning would improve after six months due to the clinical care the clinical participants received, and the fact that psychotic symptoms are often found to be transitory (Van Os et al., 2009). Further, psychotic and depressive symptoms were anticipated to co-occur and impact on each other (Wigman et al., 2012), and psychotic symptoms at baseline to predict psychotic symptoms and other clinical measures after 6 months, based on the finding that psychotic symptoms are not only a risk factor for developing psychosis but also other psychopathology (Kelleher et al., 2012c; Rössler et al., 2011). Finally, clinical symptoms were expected to be positively associated with each other, and negatively associated with functioning over time.

3.2 Methods

3.2.1   Participants & procedure

All 73 clinical participants who were help-seeking and experiencing psychological distress participated in this study. Recruitment, inclusion and exclusion criteria for clinical participants are described in Section 2.2 and the study procedure is described in Section 2.3 in detail.

3.2.2   Treatment interventions

35 clinical participants were taking antidepressant medication and an additional five were prescribed other (valproic acid, anticonvulsant, and antipsychotic) medication for treatment of psychiatric conditions at baseline. One participant had reported a diagnosis of epilepsy, but did not receive anticonvulsant medication due to being seizure-free for years. No other participant reported a diagnosis of epilepsy. 42 clinical participants were receiving counselling or some sort of therapy (e.g. cognitive-behavioural or -analytic therapy) and 18 were referred, attended triage meetings or were on the waiting list for therapy.

3.2.3   Measures

Demographic information (age, gender, ethnicity, occupation and highest qualification, relationship status and whether being a parent) and information on clinical and functioning measures was gathered via interview and self-report. These information included psychotic (CAARMS), depressive (QIDS), and anxiety (OASIS) symptoms, psychological distress (K-10), and functioning (Global functioning: Social and Role scale) as described in Section 2.4. Obtaining total scores of the employed measures and classification of UHR status followed the same procedure as described in Sections 2.4 and 2.5.

In order to establish whether UHR clinical participants differ in clinical features, such as depressive and anxiety symptoms, and functioning from clinical participants who experience psychological distress but do not fulfill UHR criteria, the sample was classified in

clinical participants with UHR status (n = 16) and clinical participants without UHR status ("non-UHR clinical participants", n = 53). 4 individuals met criteria for a psychotic episode at baseline assessment according to the CAARMS, and were submerged with UHR (n = 16+2) and non-UHR (n = 53+2) individuals. Individuals with subclinical psychotic symptoms but without a 30% drop in functioning/chronic low functioning were referred to as *PLE*. All constellations of an intensity and frequency of less than 3 were considered as *no significant psychotic symptoms.*

3.2.4 Statistical Analysis

Independent samples t-tests and analyses of variance (ANOVA) were used when conducting group comparisons of age and total scores of clinical measures, where parametric assumptions were met. Otherwise, Mann-Whitney U-tests and Kruskal-Wallis tests were conducted. For analysis of categorical data, such as gender, ethnicity, occupation and highest education, x^2- tests were used to evaluate group differences. Paired t-tests and Wilcoxon Signed Ranks tests were further employed to longitudinally analyse clinical symptoms and functioning from baseline to 6 months and repeated measures ANOVA and Friedman tests from baseline to 3 and 6 months. One-way ANOVA were used to disentangle the influence of (sub)clinical psychotic symptoms on functioning. Multiple linear and hierarchical regressions were conducted to investigate which clinical symptoms potentially predict depressive and psychotic symptoms at 6 months, and whether psychotic, depressive, and anxiety symptoms at baseline predicted social and role functioning after 6 months, and whether functioning predicted clinical outcomes at 6 months.

3.3 Results

3.3.1 Demographics and UHR vs non-UHR group comparison

The total sample (n = 73, 51 females) had a $M_{age} \pm$ SD of 20.6 ± 2.6 years and was predominantly White-British. UHR individuals only differed from non-UHR[1] clinical participants concerning their relationship status with more UHR clinical participants being in a relationship than non-UHR, and a better role functioning in non-UHR clinical participants than UHR. There were no further significant differences concerning demographics such as age, gender, ethnicity, occupation, highest level of education, or concerning depressive and anxiety symptoms, general distress or social functioning at baseline (see Table 3.1).

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[1] For the purpose of this analysis, of the non-UHR clinical participants (n=55), 15 individuals were categorised as individuals with PLE and 40 as no significant psychotic symptoms, as opposed to individuals classified as UHR (n=18).

Table 3.1

Demographic information, clinical measures, and functioning scores for the total sample, and comparing UHR clinical participants with clinical participants who are not at UHR for psychosis at baseline

	Total sample (n=73)	UHR (n=18)	Non-UHR (n=55)	Test statistics
Demographics				
Age (M±SD) in years	20.6±2.6	20.9±3.0	20.5±2.5	t(71)=-0.52, p=0.60
Gender (m/f)	22/51	5/13	17/38	$X^2(1)$=0.63, p=0.80
Ethnicity				
White[1]	61	16	45	
Asian[2]	3	1	2	
Black[3]	3	0	3	$X^2(3)$=1.39, p=0.71
Mixed-race[4]	6	1	5	
Occupation				
University student[5]	18	1	17	
College/A-Levels	22	5	17	
Unemployed	17	3	9	$X^2(4)$=7.46, p=0.11
Employed[6]	12	7	10	
Homemaker	4	2	2	
Highest qualification				
University[7]	6	1	5	
A-Levels[8]	33	7	26	$X^2(3)$=1.47, p=0.69
GSCE[9]	28	9	19	
No qualification	6	1	5	
Relationship status				
Single/relationship	44/29	6/12	38/17	$X^2(1)$=7.24, p=0.01**
Having children (yes/no)	9/63	3/15	6/48	$X^2(1)$=0.38, p=0.54
Clinical measures				
QIDS score (M±SD)	10.9±4.1	10.4±3.8	12.2±4.8	t(71)=-1.57, p=0.12
Range	3-19			
K10 score (M±SD)	30.7±8.1	30.4±8.2	31.5±7.8	t(68)=-0.50, p=0.62
Range	10-50			
OASIS (M±SD)	9.3±4.6	8.9±5.5	9.6±4.5	t(67)=0.47, p=0.64
Range	0-20			
Functioning				
Social Functioning (Median)	7	6	7	U=409.5, Z=-1.12, p=0.26
Range	3-9			
Role Functioning (Median)	6	3	7	U=329, Z=-2.15, p=0.03*
Range	1-9	3	7	

Notes. UHR=ultra-high risk*, M=mean, SD=standard deviation, m=male, f=female, [1] White-British & White-Other, [2] Asian-Pakistani, Asian-Bangladeshi & Other Asian, [3] Black-African, [4] Mixed-Race White-Black-Caribbean, [5] Undergraduate and postgraduate university students, [6] Working full or part-time, [7] Bachelor or Master degree, [8] A-Levels, National Vocational Qualification (NVQ) Level 4, or equivalent, [9] General Certificate of Secondary Education (GCSE, year-10 equivalent) or NVQ level 1 or 2, ** p < 0.01.

Clinical participants who did not participate in the 6 months follow-up assessment (n = 18) did not differ significantly from the original baseline sample (n = 73) concerning demographics and clinical measures at baseline (see Table 3.2), indicating that drop-out rates did not influence the results presented in the following.

Table 3.2

Comparison of baseline demographic information and baseline clinical measures between baseline sample and those who were not followed up

	Baseline (n=73)	No follow-up (n=18)	Test statistics	p-value
Demographics				
Age (M±SD) in years	20.6±2.6	20.1±2.5	t(89)=0.4	0.41
Gender (m/f)	22/51	5/13	$X^2(1)$=0.4	0.84
Ethnicity				
White[1]	61	13		
Asian[2]	3	0	$X^2(3)$=3.61	0.31
Black[3]	3	1		
Mixed-race[4]	6	4		
Occupation				
University student[5]	18	0		
College/A-Levels	22	8		
Unemployed	12	2	$X^2(4)$=6.87	0.14
Employed[6]	17	6		
Homemaker	4	2		
Highest qualification				
University[7]	6	1		
A-Levels[8]	33	5	$X^2(3)$=3.9	0.27
GSCE[9]	28	8		
No qualification	6	4		
Relationship status				
Single/relationship	44/29	8/10	$X^2(1)$=0.13	0.72
*Having children (*yes/no)	9/63	4/13	$X^2(1)$=1.34	0.25
Clinical measures				
CAARMS total (M_{score}±SD)	13.7±8.3	13.8±6.6	t(89)=0.08	0.94
QIDS (M_{score}±SD)	10.9±4.1	11.6±5.1	t(89)=0.61	0.54
Social Functioning (Median)	7	6	U=650.5, Z=-0.67	0.95
Role functioning (Median)	6	6	U=608.5, Z=-0.49	0.62
OASIS (M_{score}±SD)	9.3±4.6	9.5±5.9	t(89)=0.16	0.87
K-10 (M_{score}±SD)	30.7±8.1	31.3±9.8	t(89)=2.5	0.8

Notes. M=mean, SD=standard deviation, m=male, f=female, [1] White-British & White-Other, [2] Asian-Pakistani, Asian-Bangladeshi & Other Asian, [3] Black-African, [4] Mixed-Race White-Black-Caribbean, [5] Undergraduate and postgraduate university students, [6] Working full or part-time, [7] Bachelor or Master degree, [8] A-Levels, National Vocational Qualification (NVQ) Level 4, or equivalent, [9] General Certificate of Secondary Education (GCSE, year-10 equivalent) or NVQ level 1 or 2, CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory of Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale.

Depressive and anxiety symptoms, psychological distress and social and role functioning at baseline did not differ significantly between clinical participants with no significant psychotic symptoms, UHR clinical participants and individuals experiencing PLE[2] (see Table 3.3).

Table 3.3
Clinical measure scores for clinical participants with no significant symptoms, UHR clinical participants and clinical participants with PLE at baseline

Measure	No symptoms (n=40)	PLE (n=15)	UHR (n=18)	Test statistics	Effect size[1] η^2
QIDS score M±SD	10.3±3.5	10.7±4.6	10.9±4.6	F(2,70)=1.27, p=0.29	0.035
K-10 score M±SD	30.2±7.6	31.0±9.6	31.5±7.8	F(2,67)=0.18, p=0.84	0.005
OASIS M±SD	9.1±4.2	10.1±5.3	9.0±4.8	F(2,70)=0.27, p=0.76	0.008
Social Functioning Median	7	6	6	X^2(2)=1.64, p=0.44	0.023
Role Functioning Median	7	6	3	X^2(2)=4.70, p=0.10	0.062

Notes. UHR=ultra-high risk, PLE=psychotic-like experiences, QIDS=Quick Inventory of Depressive Symptoms, K-10=Kessler Psychological Distress Scale, M=mean, SD=standard deviation, OASIS=Overall Anxiety Severity and Impairment Scale.
[1] For practical reasons all effect sizes have been calculated assuming the data meets parametric assumptions.

3.3.2 Development of (sub)clinical psychotic symptoms

At baseline, 40 clinical participants (54.8%) presented with no significant psychotic symptoms (6 of those scoring 0 on all subscales), 13 experienced PLE (17.8%), whereas another 16 individuals were classified as UHR for psychosis (21.9%) and 4 clinical participants fulfilled criteria for a psychotic episode (5.5%). Table 3.4 illustrates the development of all four groups after 6 months: the majority of the sample remained without

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[2] Clinical participants with psychotic symptoms according to the CAARMS at baseline (n=4) were submerged with UHR clinical participants (n=16) and clinical participants with PLE (n=13) due to the small sample size, depending on whether clinical participants experienced a drop in functioning/chronic low functioning or not, resulting in 18 UHR clinical participants and 15 clinical participants with PLE.

significant psychotic symptoms (30.1%), 13.7% developed subclinical psychotic symptoms, 13.6% with subclinical psychotic symptoms at baseline remitted to no significant psychotic symptoms, 10.9% remained with subclinical psychotic symptoms, 2.7% transitioned to threshold psychotic symptoms and 4.1% remitted from threshold to subclinical psychotic symptoms. 24.7% of individuals were lost for follow-up.

Table 3.4
Development of (sub)clinical psychotic symptoms after 6 months in percentages (%)

T1 T2	no symptoms[1]	PLE	UHR	Psychotic
no symptoms[1]	30.1	6.8	6.8	0
PLE	5.5	1.4	0	0
UHR	8.2	2.7	6.8	4.1
psychotic	0	0	2.7	0
lost[2]	11	6.8	5.5	1.4

Notes. T1=Baseline, T2=6 months follow-up, UHR=ultra-high risk, PLE=psychotic-like experiences*,*
[1] no significant psychotic symptoms, [2] lost for follow-up.

3.3.3 Development of depressive and anxiety symptoms along classification of psychotic symptoms

At baseline, the majority of the sample presented with mild to moderate depressive and no significant psychotic symptoms. After 6 months, a decline in depressive symptoms was evident, with most clinical participants falling in the category of none to mild depressive and no significant psychotic symptoms. No clinical participant met criteria for very severe depressive symptoms at either time point (see Table 3.5).

Table 3.5
Severity of depressive symptoms for individuals at UHR, with PLE or no significant psychotic symptoms at baseline (T1) and after 6 months (T2) in percentages (%)

		none	Mild	moderate	severe	very severe
T1	no symptoms[1]	5.5	23.3	21.9	4.1	0
	PLE	2.7	6.8	6.8	4.1	0
	UHR	2.7	4.1	11	6.8	0
T2	no symptoms[1]	23.4	25.5	7.3	1.8	0
	PLE	3.6	7.3	1.8	3.6	0
	UHR	9.1	9.1	5.5	1.8	0

Notes. *T1=Baseline, T2=6 months follow-up,* UHR=ultra-high risk, PLE=psychotic-like experiences*,* [1] no *significant* psychotic symptoms.

Individuals were classified into having an anxiety diagnosis or not, according to OASIS total score. At baseline, the majority of clinical participants presented with an anxiety diagnosis, and no significant psychotic symptoms. Over time, this pattern changed to the majority remitting to *no* anxiety diagnosis with no significant psychotic symptoms (see Table 3.6).

Table 3.6
Frequency of anxiety diagnosis according to classification of psychotic symptoms at baseline and after 6 months in percentages (%)

		Anxiety diagnoses	No anxiety diagnosis
T1	no symptoms[1]	38.4	16.4
	PLE	12.3	8.2
	UHR	15.1	9.6
T2	no symptoms[1]	25.9	31.5
	PLE	7.4	9.3
	UHR	13	13

Notes. *T1=Baseline, T2=6 months follow-up,* UHR=ultra-high risk, PLE=psychotic-like experiences*,* [1] no *significant* psychotic symptoms.

3.3.4 Longitudinal analyses of clinical measures and functioning comparisons

Paired t-tests and Wilcoxon Signed Ranked tests revealed that clinical participants showed significant improvement in psychotic, depressive and anxiety symptoms and social functioning from baseline as compared to after 6 months, however, there was only a trend for role functioning (see Table 3.7).

Table 3.7
Longitudinal analyses of clinical measures and functioning from baseline to 6 months follow-up

	Mean BL	Mean 6 months	Test Statistic	p-value
CAARMS total	13.6	11.3	t(54)=2.18	0.033*
QIDS	10.6	7.6	Z=-4	<0.001***
Social Functioning	6.5	7.0	Z=-2.18	0.029*
Role functioning	5.3	5.7	Z=-1.73	0.083
OASIS	9.1	6.6	Z=-3.6	<0.001***
K-10	30.5	24.0	t(53)=5.33	<0.001***

Notes. CAARMS=Comprehensive Assessment for At-Risk Mental States, QIDS=Quick Inventory for Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale, * p < 0.05, *** p < 0.001.

When looking at the trajectories from baseline over 3, up to 6 months, repeated measures ANOVA and Friedman tests confirmed improvements for depressive and anxiety symptoms, a trend for social and role functioning, but no significant improvement for psychotic symptoms. Strongest improvement took place during the first three months of the follow-up period, instead of the second half (see Table 3.8).

Table 3.8
Longitudinal analyses of clinical measures and functioning from baseline, 3 and 6 months follow-up

	M±SD/ Median BL	M±SD/Median 3 months	M±SD/Median 6 months	Test Statistic	p-value
CAARMS total (n=49)	13.3±9	11.3±9.2	11.5±8.7	F(1,48)=2.35	p=0.132
QIDS (n=50)	11	8	6	X^2(2)=17.36	<0.001***
Social Functioning (n=50)	7	7	7	X^2(2)=4.98	0.083
Role functioning (n=50)	6	7	7	X^2(2)=5.7	0.058
OASIS (n=48)	9	7	7	X^2(2)=7.42	0.024*
K-10 (n=50)	30.8±7.2	25.1±7.4	24.3±8.6	F(1,49)=25.87	<0.001***

Notes. M=mean, SD=standard deviation, CAARMS=Comprehensive Assessment for At-Risk Mental States, QIDS=Quick Inventory for Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale, * $p < 0.05$, *** $p < 0.001$.

3.3.5 Co-occurrence of depressive symptoms and anxiety

Comorbidity affects more than half of all individuals with mental disorders (Clark, 1995). Section 3.3.3 illustrated how many individuals of this sample are affected by (sub)clinical psychotic and depressive or anxiety symptoms a the same time. To complete a comorbidity overview of this sample, the rates of co-occurence for depression and anxiety are the following in this cohort: 12 individuals with an anxiety diagnosis experienced mild, 22 moderate, and 11 severe depressive symptoms at baseline assessment.

3.3.6 Association between depressive and psychotic symptoms

Multiple linear regression revealed that only psychotic symptoms at baseline predicted psychotic symptoms (F (4, 49) = 8.72, p < 0.001, R^2 = 0.21, Cohen's f^2 = 0.266) and depressive symptoms at 6 months (F (4, 49) = 3.3, p = 0.018, R^2 = 0.21, Cohen's f^2 = 0.266). In the model, depressive and anxiety symptoms and general distress at baseline were not predictive for depressive and psychotic symptoms after 6 months (all p > 0.05, see Table 3.9).

Table 3.9

Summary of Multiple Regression Analysis for variables predicting psychotic and depressive symptoms at six months (n=55)

	Psychotic symptoms prediction			*Depressive symptoms prediction*		
	B	SE	β	B	SE	B
CAARMS total	0.431	0.12	0.441**	0.166	0.073	0.326*
QIDS total	0.415	0.33	0.184	0.09	0.199	0.077
OASIS total	-0.054	0.289	-0.025	0.055	0.174	0.051
K-10 total	0.209	0.17	0.186	0.076	0.102	0.13

Notes. B=Beta, SE =Standard Error, CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory for Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale, * $p < 0.05$.

3.3.7 Prediction of functioning at 6 months

Repeated measures ANOVA with baseline classification into *no significant psychotic symptoms*, PLE and *UHR status* showed no significant association with social and role functioning, and no significant interaction effect from baseline to 6 months (all $p > 0.05$). Due to the non-parametric nature of social and role functioning, Kruskal-Wallis tests were conducted, and confirmed no effect of this classification on social and role functioning at 6 months. In order to maximise power, Mann-Whitney-U-tests revealed that baseline categorisation comparing those who experience clinical or subclinical psychotic symptoms (PLE, UHR, and psychotic symptoms) with those without significant psychotic symptoms, also did not predict social and role functioning after 6 months (all $p > 0.05$).

Table 3.10

Spearman correlations (one-tailed) and p-values of clinical measures and social and role functioning at BL and 6 months (n=55)

6 months \ BL	Social	Role	CAARMS	QIDS	OASIS	K-10
CAARMS	-0.409**	-0.455**	-	-	-	-
	0.001	<0.001				
QIDS	-0.216	-0.207	-	-	-	-
	0.057	0.065				
OASIS	-0.103	-0.282*	-	-	-	-
	0.229	0.019				
K-10	-.0158	-0.36*	-	-	-	-
	0.125	0.033				
Social[1]	-	-	-0.367**	-0.28*	-0.406**	-0.349**
			0.003	0.019	0.001	0.005
Role[2]	-	-	-0.417**	-0.255*	-0.18	-0.326**
			0.001	0.03	0.094	0.008

Notes. BL=baseline*,* CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory for Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale, [1] Social functioning, [2] Role functioning, * $p < 0.05$, ** $p < 0.01$.

One-tailed Spearman correlations revealed, as hypothesised, significant negative correlations between baseline clinical measures and social and role functioning at 6 months (see Table 3.10). A linear regression showed that CAARMS, QIDS, OASIS, and K-10 at baseline were significant in predicting social functioning at 6 months ($F_{(4, 49)} = 4.34$, $p = 0.004$, $R^2 = 0.262$, Cohen's $f^2 = 0.355$) and role functioning at 6 months ($F_{(4, 49)} = 4.202$, $p = 0.005$, $R^2 = 0.255$, Cohen's $f^2 = 0.342$). These effects were driven by CAARMS total score for social ($p = 0.019$) and role functioning ($p = 0.003$), and partly via a trend for OASIS total score ($p = 0.058$) for social functioning ($p > 0.05$, for all other scores).

A hierarchical multiple linear regression analysis was then conducted, in order to control for the effect of functioning at baseline, when predicting functioning at 6 months. Baseline social and role functioning was included in block 1 and baseline clinical symptom scores in block 2. The analysis revealed a significant prediction for block 1 ($F_{(1, 51)} = 20.23$, $p < 0.001$, $R^2 = 0.442$) and block 2 ($F_{(6, 47)} = 7.41$, $p < 0.001$, $R^2 = 0.486$) with social

functioning at 6 months as dependent variable. However, only lower social functioning at baseline significantly predicted lower social functioning at 6 months ($p < 0.001$) (see Table 3.11). The effect size attributable for the addition of block 2 is Cohen's $f^2 = 0.117$. A hierarchical multiple linear regression analysis with baseline social and role functioning in block 1 and baseline clinical symptom scores in block 2, and role functioning at 6 months as dependent variable, revealed a significant prediction for block 1 ($F (1, 51) = 30.59$, $p < 0.001$, $R^2 = 0.545$) and block 2 ($F (6, 47) = 6.47$, $p < 0.001$, $R^2 = 0.58$). The effect size attributable for the addition of block 2 is Cohen's $f^2 = 0.083$. Role functioning at baseline significantly predicted role functioning at 6 months, and social functioning at baseline demonstrated a trend in predicting role functioning at 6 months ($p = 0.08$), however, no clinical measure significantly predicted role functioning at 6 months (all $p > 0.05$) (see Table 3.11).

Table 3.11
Summary of Multiple Regression Analysis for functioning and clinical variables predicting social and role functioning at six months (n=53)

	Social functioning prediction			Role functioning prediction		
	B	SE	B	B	SE	B
Social functioning	0.554	0.11	0.588***	0.319	0.178	0.188
Role functioning	0.086	0.068	0.147	0.673	0.111	0.637***
CAARMS total	-0.038	0.023	-0.213	-0.053	0.037	-0.164
QIDS total	0.036	0.058	0.087	0.062	0.095	0.083
OASIS total	-0.054	0.053	-0.139	0.088	0.086	0.126
K-10 total	-0.006	0.032	-0.03	-0.007	0.051	-0.02

Notes. B=Beta, SE =Standard Error, CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory for Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale, *** $p < 0.001$.

3.3.8 Prediction of clinical measures at 6 months

Role functioning at baseline was associated with CAARMS, OASIS and K-10 total score at 6 months and social functioning at baseline with CAARMS total score at 6 months (see Table 3.10). Multiple linear regression analyses revealed that social and role functioning was predictive of psychotic symptoms after 6 months ($F (2, 52) = 7.7$, $p = 0.001$,

$R^2 = 0.23$, Cohen's $f^2 = 0.23$), but not for depressive and anxiety symptoms (all $p > 0.05$, see Table 3.11). Hierarchical regression with the respective clinical measure at baseline in block 1 and social and role functioning at baseline in block 2, showed significant predictions for block 1, respectively, but no significant prediction for psychotic, depressive and anxiety symptoms after 6 months, indicating that social and role functioning do not predict clinical variables. This finding has been confirmed by the calculation of effect sizes: the effect size attributable for the addition of block 2 for depressive symptoms revealed a Cohen's f^2 of 0.026) and for psychotic symptoms of a Cohen's f^2 of 0.102.

3.4 Discussion

The present study quantified and monitored clinical symptoms and their interaction over time with each other and with functioning, in a sample of young, help-seeking individuals with mental health issues. Even though clinical participants were mainly recruited from *general* (and not UHR-specific) early intervention services, 1/4 were classified as UHR for psychosis and an additional 1/5 as experiencing PLE. No difference was found between UHR and non-UHR clinical participants concerning the severity of depressive and anxiety symptoms and social functioning. Both baseline and 6 months assessments displayed a similar distribution of individuals with and without some sort of psychotic symptoms, however, clinical participants showed a dynamic pattern of transition and remission. Social and role functioning and clinical symptoms were associated with each other from baseline to 6 months. No robust prediction could be revealed, and if so, associations were mainly discovered for psychotic symptoms as compared to depressive and anxiety symptoms, but only when a total score index of psychotic symptoms was included as compared to psychosis classifications. The best predictor for social and role functioning at 6 months appeared to be social and role functioning itself, respectively, with social functioning also displaying a trend in predicting role functioning but not the other way round. Overall, the whole population improved after 6 months, with most improvement happening during the first 3 months of the follow-up period.

The finding of 17% transition rates from UHR status to threshold psychotic symptoms and 17% of UHR persistence rates after 6 months, are comparable to previous literature with transition rates to psychosis of 22% after one year (Fusar-Poli, 2012) and 3-year persistence rates of psychotic symptoms of up to 31% (Cougnard et al., 2007). Rates of 39% of individuals with sub-threshold psychotic symptoms and 6% with frank psychotic symptoms, and classification of the majority of the sample as experiencing mild to moderate depressive symptoms, are comparable with rates of a study conducted in a similar setting in Australia (Purcell et al., 2014). The finding that the majority of developmental psychotic experiences in childhood and adolescence are transient (Van Os et al., 2009) is consistent with the findings

of remission of 3 out of 4 individuals of the current sample, remitting to subclinical psychotic symptoms after experiencing threshold psychotic symptoms at baseline, and about one third at UHR and experiencing PLE remitting to no significant psychotic symptoms. The improvement concerning psychotic symptoms and overall symptomatology and functioning at follow-up might well be due to the clinical care that participants had received (e.g. medication and psychological interventions). However, neither standardised treatments nor a waiting-list control group were implemented that could verify the effect of treatment on the overall improvement of the sample.

Neither help-seeking youths with diffuse mental health problems who were classified as UHR and non-UHR, nor UHR individuals and those with PLE differed significantly concerning depressive and anxiety symptoms and social functioning. This supports the idea that psychological distress and social impairment appears to be equally present in all sub-groups. However, non-UHR clinical participants presented with significantly better role functioning. This has been confirmed when calculating effect sizes: there were only small effect sizes for depressive and anxiety symptoms, psychological distress and social functioning; however, there was a medium effect size for role functioning. Altogether, this indicates that the required drop in functioning or chronic low functioning for defining UHR status is rather driven by role instead of social functioning. The inclusion of a functioning drop/chronic low functioning for the definition of UHR status may be helpful in enriching the number of actual transitions to psychosis for conceptual purposes (Yung et al., 2008), but does not appear to be an indicator of actual need for treatment and clinical care. It actually emphasises that individuals who are generally at risk for developing mental health disorders, should not be neglected in terms of clinical care since their symptomatology appears to be equally relevant to UHR samples. It remains to be longitudinally investigated whether non-UHR clinical populations are equally at risk for developing severe, non-psychotic mental disorders.

The present study confirms other work that depressive and psychotic symptoms often co-occur (Kelleher et al., 2012b; Wigman et al., 2012), as almost the whole sample

displayed at least some mild or low frequency psychotic symptoms, and only 6 out of 73 clinical participants did not present with any sort of psychotic symptoms. Psychotic symptoms further seem to predict both psychotic and depressive symptoms at 6 months, which is in agreement with the finding that these mental states mutually affect each other (Wigman et al., 2012), however, this data suggests that psychotic symptoms rather affect other mental states (such as depressive and anxiety symptoms) than the opposite direction.

Wigman et al. (2014) found that patients with non-psychotic psychiatric disorders but additional psychotic symptoms showed lower global functioning than those without psychotic symptoms. The current study validates this finding and the interpretation that psychotic symptoms complicate anxiety and depressive disorders (Wigman et al., 2012), as only psychotic, but neither depressive nor anxiety symptoms at baseline, significantly predicted psychotic and depressive symptoms at follow-up. Effect size calculations confirmed this effect of psychotic symptoms at baseline predicting psychotic and depressive symptoms at 6 months with medium to large effect sizes. Further, the prediction of social and role functioning at follow-up by means of clinical baseline measures revealed that psychotic symptoms were the only significant predictor in the model. The overall model achieved large effect sizes. Therefore improving coping skills might be a target for early intervention that may contribute to better clinical and functional outcomes in patients who are presenting with psychotic symptoms (Wigman et al., 2014). Clinical symptoms at 6 months were predicted with medium to large effect sizes by social and role functioning; however, this effect disappeared when controlling for social and role functioning in a hierarchical regression, achieving only small effect sizes. Similarly, the effect of clinical (especially psychotic) symptoms being predictive for functioning disappeared when controlling for clinical symptom scores in a hierarchical regression, which has also been confirmed by a reduction in effect sizes to small to medium.

Considering recent transition rates (Fusar-Poli, 2012) and the finding that the majority of psychotic symptoms in childhood are transient (Van Os et al., 2009), not everybody who is at risk for developing psychosis will eventually transition to a psychotic illness. In fact, this at-risk state may indicate a rather general underlying tendency toward common mental disorders (Rössler et al., 2011), instead of proneness to psychosis only. However, given the impairment associated with schizophrenia and other mental disorders, it is important to unravel risk factors, for those who are going to have adverse mental health outcomes. One factor that might be associated with transition is the age of at-risk individuals. Bartels-Velthuis, van de Willige, Jenner, van Os, and Wiersma (2011) demonstrated that auditory hallucinations in early adolescence were strongly predictive of psychopathology, as compared to only a minor association when assessed during childhood. This finding was independent of whether psychotic symptoms were persistent or newly occurring, implying that psychotic symptoms may need to be more closely monitored during adolescence, and posing a greater risk factor for developing mental health problems, as compared to when occurring during childhood.

It can further be said, that such vulnerability markers indicate not only risk for future psychosis (and other mental disorders), but also constitute a clinical condition that requires treatment itself (Cornblatt et al., 2003). This notion is confirmed by the clinical description of the current sample, considering that individuals mainly presented with rather general depressive and anxiety symptoms and either sub-clinical psychotic symptoms equivalent to UHR description (Yung et al., 2005), or of even less intensity and frequency. All clinical participants were so affected by their clinical symptoms and associated distress and impairment, that they were seeking help from secondary mental health care professionals.

There were several limitations to the current study. Similarly to Hickie et al. (2013), clinical assessments were conducted by a number of different researchers, and treatments provided were not standardised, and not available for all clinical participants. The cohort was

followed-up within only six months, though the data show that in adolescence and early adulthood, even such a short time period can coincide with multiple personal developments and happenings, both positively and negatively affecting mental health outcomes, well-being and functioning, without requiring a more extensive follow-up period.

The implemented interview and self-report measures comprise different time windows for symptom assessment, and therefore might encompass dissimilar impact. For example, the QIDS captures depressive symptoms in the past week only, whereas the CAARMS refers to psychotic symptoms in the past year. This gives the CAARMS the opportunity to yield a comparatively higher total score, since symptoms can accumulate over one year as compared to accumulation over one week only. Therefore, the impact of psychotic symptoms might be over-represented for prediction of symptoms and functioning at follow-up.

Even though the sample was quite small for a cohort study, it was decently sized and given the detailed and comprehensive psychopathological assessments that were conducted. Effect size calculations overall confirmed findings of statistical tests. The sample comprised of a very heterogeneous clinical presentation. Across the sample, almost the whole continuum of all dimensional measures was covered, indicating that participants differed widely from none to severe symptom presentation across diagnostic categories. However, the presented findings are not fixed to diagnostic categories during the early stages of mental health, constituting a different approach to mental health, that aims to circumvent issues around comorbidity (Clark, 1995) and the question of the existence of natural boundaries between mental disorders (Kendell & Jablensky, 2003), which constitutes a main advantage of this study using this approach. Lastly, psychiatric medication intake was not controlled for, and the majority of the sample was taking antidepressant medication or medication addressing psychotic experiences and symptoms of bipolar disorder. Medication intake may have affected the results of this study; however, the study was built on an approach looking at mental health issues in their natural occurrence without specific selection and inclusion criteria.

In conclusion, the current study emphasised the importance of looking at youth mental health from a dimensional perspective. Psychotic, depressive and anxiety symptoms and functioning were, as expected associated with each other, yet, no robust predictions for future clinical and functional outcomes can be made; of all measures used, psychotic symptoms appear to be most predictive, however only when looked at on a continuum instead of using classification systems.

CHAPTER FOUR

LONGER-TERM INCREASED CORTISOL LEVELS

Disturbance of HPA axis activity is commonly reported in a range of mental disorders by means of point measures such as blood, saliva and urine samples. These short-term indices do not account for potential damaging effects of longer-term increased cortisol levels. Hair strands of 30 young people (16-25 years) presenting with mental health problems ($M_{age} \pm$ SD = 20.9 ± 2.5, 26 females) and 28 healthy controls (HC, $M_{age} \pm$ SD = 20 ± 2.9, 26 females) were analysed for cortisol concentrations, representing the past 3 (hair segment 1) and 3 to 6 (hair segment 2) months prior to hair sampling. Clinical participants completed a semi-structured interview and self-report assessment on psychiatric symptoms, functioning and lifestyle factors. All participants completed the Perceived Stress Scale. Hair cortisol concentrations representing the past 3 (but not 3 to 6) months were significantly increased in clinical participants compared to HC. Perceived stress in the past month was significantly higher in clinical participants compared to HC, but was not significantly correlated with hair cortisol concentrations. Hair cortisol levels were only significantly associated with psychological distress but no other psychiatric symptoms, functioning and lifestyle indices. Hair segment analyses revealed longer-term increased levels of cortisol in the past 3 months in young people with early mental health problems. Further insight into the role of cortisol on the pathogenesis of mental illnesses requires longitudinal studies relating cortisol to psychopathology and progression of illness.

4.1 Introduction

Disturbances in HPA axis diurnal activity and responsivity are common findings in a range of mental disorders (e.g. Knorr, Vinberg, Kessing, & Wetterslev, 2010; Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007; Yehuda, Boisoneau, Mason, & Giller, 1993). One of the most commonly reported parameters of the HPA axis is the glucocorticoid hormone cortisol. Over- and under-activity of cortisol concentrations have been reported by means of blood, saliva and urine samples in mood disorder (Cervantes, Gelber, Kin, Nair, & Schwartz, 2001; Vreeburg et al., 2009), psychosis (Ryan, Sharifi, Condren, & Thakore, 2004), posttraumatic stress disorder (PTSD) (Yehuda et al., 1990), panic disorder (Bandelow et al., 2000) and GAD (Mantella et al., 2008), somatisation syndrome (Rief, Shaw, & Fichter, 1998), and eating (Monteleone et al., 2001) and substance use (Adinoff, Ruether, Krebaum, Iranmanesh, & Williams, 2003) disorders. Despite this, there is considerable variability across (Yehuda et al., 1993) and within diagnostic categories (for meta-analyses in depression, see Knorr et al., 2010; and PTSD, see Meewisse et al., 2007), which is why it is important to investigate whether cortisol fluctuations can be explained by other factors as well, such as inter-individual differences and stressor characteristics (Miller, Chen, & Zhou, 2007).

Stalder and Kirschbaum (2012) reviewed the analysis of cortisol in hair and stated that established analyses of cortisol in *saliva*, *plasma,* and *urine* have proven to be useful and reliable tools for documenting *real-time* circulating cortisol levels (*plasma*, *saliva*) or mean cortisol excretions over a specific time, usually 24 hours (*urine*). In contrast to this, *hair* cortisol represents a reliable, *longer-term* measure (generally up to months) to gauge stress and endogenous cortisol concentrations. The advantages of hair cortisol assessments lie in providing a retrospective calendar of hair cortisol levels over an extended time period that is virtually not possible to achieve with any other of the previously reported methods. It further constitutes a non-invasive sampling method, samples can be easily stored at room temperature for an extended time period, and sampling avoids problems of adherence as often experienced with, e.g. saliva samples. However, hair cortisol concentrations decrease

from more proximal to distal segments in human scalp hair, limiting the retrospective period of examination (Stalder & Kirschbaum, 2012).

Considering a generally accepted human scalp hair growth rate of 1cm per month (Wennig, 2000) and taking hair samples from the scalp-near posterior vertex region, this method allows for retrospective capture of cortisol concentrations for up to 6 months (Dettenborn et al., 2012). Recent studies in clinical populations have demonstrated increased hair cortisol concentrations in depression (Dettenborn et al., 2012), post-traumatic stress disorder (PTSD) (Steudte et al., 2011a), and in alcohol-dependent individuals (Stalder et al., 2010), and decreases in GAD (Steudte et al., 2011b), and PTSD (Steudte et al., 2013). Occupational impairment in terms of unemployment has further been shown to be associated with increased hair cortisol (Dettenborn, Tietze, Bruckner, & Kirschbaum, 2010). Strong test-retest associations for repeated hair cortisol measurements have been revealed, indicating high intra-individual stability. Structural equation modelling showed that, if no major life events or other stressors are present, hair cortisol assessments comprise a strong trait component which explains between 59-82% of variance in cortisol levels (Stalder et al., 2012). A recent systematic review on hair analyses revealed variations in hair cortisol (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013) that are similar to aforementioned meta-analyses and reviews on more established cortisol measures (Knorr et al., 2010; Meewisse et al., 2007). Despite some inconsistencies hair cortisol appeared to be increased in depression, and decreased in anxiety disorders (Staufenbiel et al., 2013).

The period of adolescence and young adulthood is characterised by a greatly increased vulnerability for the development of mental disorders. Half of the lifetime cases of mental disorder start by age 14 and three quarters by age 24 (Kessler et al., 2005). It is hypothesised that adolescence is accompanied by a biological sensitivity to stress and that age-related cortisol increase may trigger the expression of symptoms in vulnerable individuals (Walker et al., 2010). Higher cortisol levels predicting a higher risk of conversion to psychotic disorder in at-risk individuals, supports this hypothesis (Walker et al., 2010). The pathogenesis of childhood anxiety disorders appears similar: high levels of cortisol may

induce changes to subcortical circuits (such as involving the amygdala), which possibly make children vulnerable to developing anxiety symptoms (Muris, 2006). Rao, Hammen, Ortiz, Chen, and Poland (2008) exposed adolescents with depressive disorder and HC to psychosocial stress. Both groups showed increased cortisol levels, but individuals with depression displayed an increased and sustained cortisol response. This supports the notion that stressful events play a role in the development and maintenance of depressive symptoms (Rao et al., 2008).

The time between the onset of the disorder (or stressful or traumatic event) and hair collection appears to be a crucial element in explaining the diversity of cortisol findings. Luo et al. (2012) reported increased hair cortisol one month after a traumatic event in adolescents with PTSD, with levels decreasing after 7 months (for review, see Staufenbiel et al., 2013). Increased cortisol levels are therefore likely to reflect the on-going stress and not the disorder itself (Staufenbiel et al., 2013). A significant difference was observed between early- and late-onset bipolar disorder. Patients with a late onset disorder (≥ 30 years) presented with higher hair cortisol than the early-onset group and HC (Manenschijn et al., 2012). This finding suggests that early onset bipolar disorder may be more strongly linked to a genetic vulnerability while late onset is usually triggered by life events and stress (Staufenbiel et al., 2013). Taken together, these findings suggest that HPA axis activity is elevated at the time of stressor onset with declining cortisol levels as time passes (Miller et al., 2007). However, it is unclear what the exact timeline of these hormonal changes is, that is, for how long this hypothesised cortisol increase presumably persists, until decline (below normal) takes over.

An alternative to explaining the heterogeneity of HPA axis findings by classifying mental ill health into disorder-specific categories is to use a dimensional approach such as clinical staging (Section 1.3.2). Within this framework, mental disorders are assumed to develop from a *pluripotential state*, consisting of undifferentiated general symptoms (such as depressive and anxiety symptoms), and from a background of specific and non-specific risk factors (Lin et al., 2013; McGorry et al., 2006), which are associated with non-specific

distress (McGorry, 2013). This idea is supported by the recent finding of a common mental distress factor underlying depressive, anxiety, and psychotic phenomena in adolescents (Stochl et al., 2015). It can therefore be inferred from the clinical staging model that the early stages of mixed mental health problems are coinciding with elevated cortisol levels. There has been no such study that has looked at longer-term cortisol levels in youth with early mental health problems from a clinical staging perspective.

The aim of this study was to investigate the pathogenesis of mental disorders in adolescents and young adults, and whether diverse psychiatric symptoms are associated with altered longer-term cortisol levels. Young people were included who had sought help for mental health problems, as well as HC. The hypothesis was tested whether early stages of mental health problems are associated with significant distress (McGorry, 2013) and therefore elevated cortisol levels. The association between cortisol levels and general psychological distress, depressive, anxiety, and psychotic symptoms, alcohol and tobacco use, and childhood traumatic experiences was further investigated.

4.2 Methods

4.2.1 Participants & Procedure

Thirty-one clinical participants and 28 HC were included in this study. Clinical participants from the main study as described in Chapter 3, who either had a family history of mental health problems or those who felt their mental health problems did not improve 6 weeks after the baseline clinical assessment, were asked to take part in this study. Clinical participants were either approached during or after the interview if they had a family history, or given a telephone call 6 weeks after and explained the neurobiological assessments. HC were recruited via staff from university and local advertisements. HC were age, gender, occupation and education matched to the clinical participants, and had no personal or first-degree family history of mental illness. A personal history was excluded by using the Structured Clinical Interview for DSM-IV-TR (American Psychiatric Association, 2000) Axis I Disorders. Exclusion criteria for both groups were a hair length of less than 3 cm at the posterior vertex region, a lack of sufficient English and cognitive ability to provide informed consent and adequately complete assessments. The study was approved by the local research ethics committee and participants provided written informed consent.

4.2.2 Measures

Demographic information (age, gender, ethnicity, occupation and highest qualification) and information on clinical and functioning measures was gathered via interview and self-report. These information included psychotic (CAARMS), depressive (QIDS), and anxiety (OASIS) symptoms, psychological distress (K-10), and functioning (Global functioning: Social and Role scale) as described in Section 2.4. Obtaining total scores of the employed measures and classification of UHR status followed the same procedure as described in Sections 2.4 and 2.5.

Information on regular medication intake was collected and covered exposure to contraceptive hormones (oral intake, patches or implants) or glucocorticoids, and psychiatric

medication (antidepressants, neuroleptics, beta-blockers, anticonvulsants) in the past 6 months. All participants self-reported demographic and hair-related information (number of hair washes per week, hair treatments) and completed the 10-item Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983). The PSS evaluates the extent to which situations in one's life are appraised as stressful and the degree to which a person rates their life as unpredictable, uncontrollable, and overloading (Cohen et al., 1983). Information from the baseline assessments of the clinical group was used for the CAARMS, QIDS, OASIS, K-10, Global functioning: Social and Role scale (see Section 2.4). Information on childhood trauma, ruminative style, and lifestyle factors, which was collected during the baseline assessment as well, was further included in the analyses:

Ruminative style (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008) was measured on a 10-item scale, requiring participants to indicate on a 4-point scale how often they engage with certain thoughts when they are feeling down or depressed. Total scores range from 10 – 40.

The Childhood Trauma Questionnaire, short form (CTQ-SF) (Bernstein et al., 2003) is a 28-item instrument generating information on traumatic childhood experiences using a 5-point scale. Subscales are sexual, physical and emotional abuse, and emotional and physical neglect, with subscale scores ranging from 5 – 25, and a total score from 25-125. The CTQ demonstrates good internal consistencies with Chronbach's α ranging from 0.79 – 0.94, and high retest-reliability over up to 6 months with an intra-class correlation of 0.88, as well as concurrent validity with the Childhood Trauma Interview (Bernstein et al., 1994).

Lifestyle factors were frequency of smoking and alcohol consumption in the past 3 months, and a total score for tobacco and alcohol acuity as measured by the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk et al., 2008), and body mass index (BMI). The ASSIST is a brief screening questionnaire for hazardous, harmful and dependent use of alcohol, tobacco and other psychoactive substances (cannabis, cocaine, amphetamines, sedatives, hallucinogens, inhalants, opioids, and other non-specified drugs). It provides general information about substances people have ever

used, and in more detailed format, information about substances used in the past 3 months, problems related to peoples' substance use, risk of current and future harm and dependence, by asking 7 questions for every substance group and scoring them individually to a total score for each substance. Scores ranging from 0 to 39 can be classified into *low* (for alcohol 0 - 10, all other substances 0 - 3), *moderate* (alcohol 11-26, other substances 4-26) and *high* (all 27+) substance acuity (Henry-Edwards, Humeniuk, Ali, Poznyak, & Monteiro, 2003). The calculation of Cronbach's α revealed good inter-item correlation for the individual scales ranging from 0.77 to 0.94. Concurrent validity of the ASSIST was obtained by similar, established measures, e.g. the Addiction Severity Index with correlations for scale scores ranging from 0.76 to 0.88 (Humeniuk et al., 2008). No clinical participant reached a total score for any psychoactive substance (other than tobacco and alcohol) in the range of moderate acuity or above (except moderate acuity for six clinical participants for cannabis, and for two participants for sedatives). These categories were disregarded from further analyses due to small sample sizes.

4.2.3 Hair cortisol analyses

Hair strands of approximately 3mm diameter were taken from a posterior vertex position, as close to the scalp as possible. Cortisol concentrations were determined from the hair segment most proximal to the scalp (hair segment 1; 3cm in length), and the following 3cm segment (hair segment 2) in accordance with the protocol of Stalder et al. (2012) at the department of biopsychology, Technical University, Dresden, Germany. Segments were gently mixed with 2.5ml isopropanol for 3 minutes. After drying, 7.5mg of whole, non-pulverised hair was incubated in 1800µl methanol for 18 hours at 45°C. Cortisol levels were determined using a commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). H

4.2.4   Statistical analyses

Hair samples from 31 clinical participants and 28 HC were collected. Initially 57 clinical participants and 35 HC were approached, of which 5 male and 1 female were clinical participant, and 4 male and 3 female HC could not partake due to too short or too little hair, in which case hair was shorter than 3cm or cutting would have left visible marks. Whereas those males were predominantly White-British, all 4 women were either mixed-race or Black-African. 14 of the other 21 did not partake due to passive refusal, 2 moved away after being approached, 1 was too busy, and 4 did not meet criteria for the neuroimaging studies, resulting in an overall refusal rate of 47%. Data of the first hair segment of one clinical participant was excluded due to an extreme outlier (> 90 standard deviations above the mean), providing data for 30 clinical participants and 28 HC in the first hair segment, and due to short hair, data for 24 patients and 24 HC in the second hair segment. Cortisol data was positively skewed (skewness first segment = 2.6, skewness second segment = 3.73, kurtosis first segment = 7.65, kurtosis second segment = 19.24), but analysed using t-tests which are robust against violation of parametric assumptions, and ANCOVA.

Independent samples t-tests were performed for group comparisons of cortisol, age, and PSS scores between clinical participants and HC, and between clinical participants taking antidepressants and those who were not, to discern whether antidepressant treatment could be associated with alterations in cortisol concentrations. For categorical data, x^2-tests were used to evaluate group differences. Spearman correlations were conducted to discern associations of cortisol levels with clinical measures and lifestyle factors in the clinical group, and for associations between the first and second hair segment. A paired samples t-test was conducted to compare mean hair cortisol levels in the first and second segment, as well as a repeated measured ANOVA to illustrate cortisol levels' interaction over time. ANCOVA were employed to compare clinical participants and HC, with ethnicity as covariate, since groups differed significantly and ethnicity can be a confounding variable (Wennig, 2000; Wosu et al., 2015).

4.3 Results

4.3.1 Demographics & clinical description

Clinical participants and HC did not differ significantly in terms of age, gender, years of education and occupation, but differed significantly with regards to ethnicity (see Table 4.1). Median time between gathering state-specific clinical measures (QIDS, CAARMS, K-10, OASIS, functioning, smoking, alcohol consumption, BMI) and hair collection/gathering hair-related variables (PSS-scores and medication intake, and demographics for HC) was 63.5 days (range 0 - 199 days). State-specific measures, along with data on ruminative style, and childhood trauma are presented in Table 4.2.

Table 4.1
Demographic and hair-related information on clinical participants and HC

	Clinical Participants (n = 30)	HC (n = 28)	Test statistic	*p*-value
Demographics				
Age (M ± SD) in years	21±2.4	20±2.9	$t(56)=1.32$	0.19
Gender (m/f)	4/26	2/26	$X^2(1)=0.6$	0.44
Ethnicity				
White	26	16		
Asian	1	5	$X^2(3)=8.9$	0.03*
Black	2	1		
Mixed-race	1	6		
Occupation				
University student[1]	9	9		
College/A-Levels	9	8	$X^2(3)=3.92$	0.27
Unemployed	7	2		
Employed[2]	5	9		
Years of education				
>13	5	7		
13	15	14	$X^2(2)=0.83$	0.66
<13	10	7		
Hair-related variables				
Washes per week ($\tilde{x}$)	3.5	3.5	$U=372.5, Z=-0.52$	0.6
Hair treatment[3] (%)	63.3	42.9	$X^2(1)\ 2.44$	0.12
Stress questionnaire				
PSS score, *M ± SD*	26.1 ± 4.5	12 ± 5.1	$t(56)=11.20$	<0.001***

Notes. HC=healthy controls, M=mean score, SD=Standard deviation, m=male, f=female
[1] Undergraduate and postgraduate university students, [2] Working full or part-time, volunteering, and non-paid internships, [3] Hair treatment in the past 6 months (hair coloration, dye, and perm), PSS = Perceived Stress Scale, * p < 0.05, *** p < 0.001.

Table 4.2
Clinical measure, functioning scores and lifestyle factors of clinical participants

Measure	M ± SD or Median	Range
QIDS (*n*=30)	10.3±4	4–20
Ruminative Style (*n*=29)	30.7±5.2	19–40
CAARMS (*n*=30)	14.3±10	0–30
K-10 (*n*=30)	29.7±7.0	19–43
OASIS (*n*=30)	8.9±4.6	0–17
CTQ-SF (*n*=25)	50.4±18.2	27–83
ASSIST alcohol (*n*=30)	6.9±5.5	0-19
ASSIST smoking (*n*=30)	3	0-31
BMI (*n*=28)	22.7	16.9–6.4
Smoking frequency[1] (*n*=30)	"monthly"	"never" - "daily"
Alcohol consumption[1] (*n*=30)	"weekly"	"never" - "daily"

Notes. QIDS=Quick Inventory of Depressive Symptoms, CAARMS= Comprehensive Assessment of At-Risk Mental States, K10=Kessler Psychological Distress Scale, OASIS=Overall Anxiety Severity and Impairment Scale, ASSIST= Alcohol, Smoking and Substance Involvement Screening Test, BMI=Body Mass Index, M=mean score, SD=Standard deviation, [1] Median scores for smoking and alcohol consumption frequency in the past three months are calculated based on self-report data ranging from 0 (never), 2 (once or twice), 3 (monthly), 4 (weekly), and 6 (daily or almost daily).

23 clinical participants described their major mental health problem(s) as depression, 4 as bipolar disorder, 13 as anxiety, 2 as eating disorders, 1 as obsessive-compulsive disorder, 10 were classified as UHR for psychosis, and 20 reported to have self-harmed, and 18 to have attempted suicide.

4.3.2 Hair cortisol and perceived stress: Clinical participants vs HC

There was a significant elevation of cortisol concentrations for clinical participants compared to HC for the first hair segment, representing the past 3 months of exposure prior to sampling (t (56) = 2.489, p = 0.016, d = 0.66) (see Figure 4.1, A). There were no group differences in cortisol levels for the second segment representing the past 3 to 6 months prior to sampling (p = 0.495, d = 0.2). Repeated analyses without individuals taking

glucocorticoids did not change the findings for the first (t (54) = 2.501, p = 0.015) and second segment (p = 0.473). Clinical participants perceived significantly more stress in the past month compared to HC (t (56) = 11.202, p < 0.001) (see Table 1); however, there were no statistically significant correlations between cortisol concentrations in the first segment and perceived stress, for the whole sample (r = 0.219, p = 0.099) or groups compared individually ($r_{Clinical}$ = 0.144, p = 0.448; r_{HC} = -0.201, p = 0.305). Hair cortisol of the first and second hair segment significantly correlated with each other (r_{48} = 0.286, p = 0.049). A paired-samples t-test did not reveal a significant decrease of cortisol over time (t (47) = 1.601, p = 0.116). There was no significant Group x Time interaction of cortisol levels (F (1, 46) = 1.704. p = 0.20; see Figure 4.1, B). The main finding of elevated cortisol concentrations in the first hair segment in clinical participants compared to HC remained significant after controlling for ethnicity (F (1, 55) = 4.77, p = 0.012).
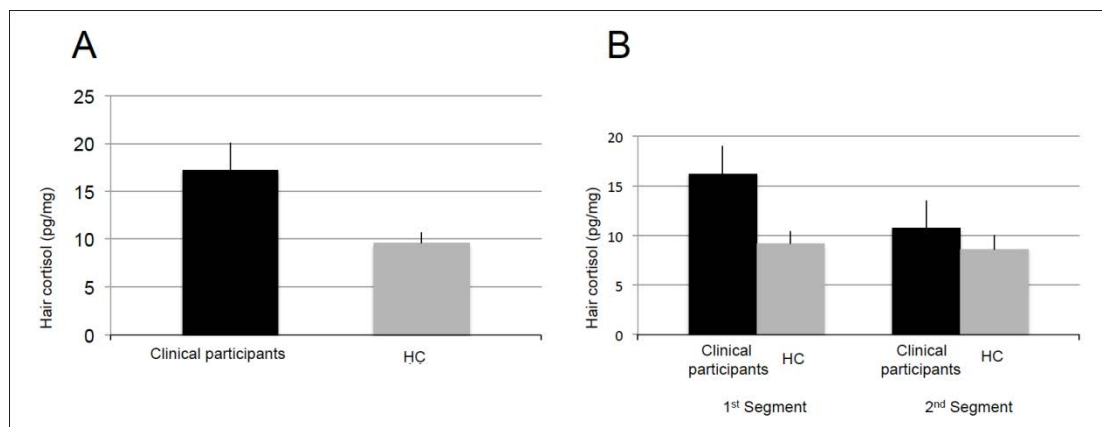
Figure 4.1. (A) Hair cortisol concentrations (1st segment) in clinical participants with mental health problems (n=30) compared to healthy controls (HC; n=28, p 0.016); (B) decrease in hair cortisol in clinical participants and HC from first ($n_{Clinical}$=24; n_{HC}=24) to second hair segment ($n_{Clinical}$=24; n_{HC}=24).

4.3.3 Hair cortisol, clinical measures, functioning, and lifestyle

Hair cortisol concentrations in the first segment were significantly correlated with K-10 total score (r = 0.506, p = 0.005, n = 29), and a trend existed for QIDS total score (r = 0.353, p = 0.052, n = 30), and Ruminative Style score (r = 0.312, p = 0.099, n = 29). No

further correlations were observed with measures and first and second hair segment (all $p >$ 0.05).

4.3.4 Hair cortisol and medication

Both groups were matched in terms of glucocorticoid and contraceptive hormone use, making this unlikely to account for group differences in cortisol in the first hair segment: One clinical participant and one HC were using glucocorticoids at the time of hair collection, of which neither produced abnormally elevated cortisol levels in either hair segment. 24% of the clinical participants and 36% of HC were exposed to contraceptive hormones at the time of hair collection.

72% of the clinical participants were taking antidepressants, 3.4% neuroleptics, 3.4% anti-convulsive medication, and 3.4% were taking beta-blockers at the time of hair collection. There were no significant differences for cortisol levels in the first (1st) and second hair (2nd) segment in those clinical participants taking antidepressants and/or other psychiatric medication (n_{1st} = 21; n_{2nd} = 16) as compared to those patients who were not (n_{1st} = 9; n_{2nd} = 8) ($p >$ 0.05).

4.4 Discussion

The present study identified elevated hair cortisol concentrations representing the past 3 months prior to hair sampling in adolescents and young adults with mental health problems compared to healthy participants. Perceived stress was also elevated in clinical participants, yet, there was no correlation between cortisol and perceived stress score. There was only a significant, positive correlation between hair cortisol in the first segment and K-10 total score, and a trend for QIDS and ruminative style total score; no other significant correlations between cortisol and clinical measures, functioning and lifestyle factors were observed.

The finding of longer-term elevated cortisol levels in young individuals with mental health problems is in line with the presumption of the experience of non-specific but significant psychological distress in the early stages of mental health problems (McGorry, 2013), and therefore with dimensional approaches to mental health such as clinical staging (Lin et al., 2013; McGorry et al., 2006). This supports the idea that this state of undifferentiated symptoms in the early stages of a mental health disorder is associated with an increase in cortisol levels and self-reported stress levels. However, whether decreases in cortisol levels coincide with illness progression (dependent or independent of diagnostic category), and whether cortisol levels decline (to normal) with remission of symptoms, remains to be investigated longitudinally.

Clinical participants were experiencing their mental health problems for at least 6 months, although they had only sought help quite recently. Considering that these problems existed for quite a while before individuals actually sought help, the time when the young people started seeking help can be seen as a *crisis point*, when their problems started to worsen (possibly due to a significant event or stressor). It is possible that help-seeking behaviour can be seen as an indicator for significant worsening of individuals' mental states, with significant increases in cortisol levels only in the past 3 months, which coincided with the help-seeking behaviour. Although there was no significant time-by-group interaction, visual inspection of the data suggests a much more pronounced increase for the clinical

group. This non-significance may be due to washout effects (Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009) and inter-individually varying rates of hair growth (Wennig, 2000) that may limit detection of differences in the more distal hair segment, or possibly to insufficient statistical power.

In most previous studies, individuals with threshold mental disorders usually at the chronic stage have been investigated, whereas the current sample included help-seeking youth in the early stages of mental health problems. Specific patterns of hair cortisol alterations were reported in previous studies, e.g. increases in depression (Dettenborn et al., 2012), and (if diagnosis sustained at least in the medium term) decreases in PTSD (Steudte et al., 2013). Concerning associations with clinical, functioning, and lifestyle measures, there was only a correlation between first segment cortisol and psychological distress, and a trend for depressive symptoms and ruminative style observed. These associations are in line with the notion of cortisol being positively correlated with depressive symptoms and psychological distress, however, no further associations were observed. Given the relatively small sample size, but highly heterogeneous and comorbid sample in terms of clinical symptoms, it is conceivable that the results were masked by the interaction of symptoms with each other. Furthermore, previous studies included clinical participants with more severe symptoms than in this sample – the more narrow range in the current study may have prevented the detection of further correlations with cortisol.

However, the lack of correlations between hair cortisol and perceived stress in this study, is not an uncommon finding (Hjortskov, Garde, Orbaek, & Hansen, 2004; Stalder & Kirschbaum, 2012; Staufenbiel et al., 2013), considering one is an objective and the other an objective measure of stress. Alternative explanations for this lack of association between cortisol and the PSS are the mismatch of time frame of one month for the PSS and 3 months for the first hair segment, or possibly the lack of validity of perceived stress in increasing hair cortisol concentrations (Staufenbiel et al., 2013), e.g. that only certain characteristics of stressors might lead to an endocrine response, which may have not been reflected (Hjortskov et al., 2004).

It has been shown that hair cortisol alterations are implicated in a variety of health conditions (Staufenbiel et al., 2013), which is consistent with the finding of elevated cortisol in our sample of individuals with a range of mental health symptoms and disorders, e.g. depressive, anxiety and sub-threshold psychotic symptoms. Even though there is some evidence that cortisol might contribute to the aetiology of psychiatric conditions such as depressive symptoms (Johnson, Fournier, & Kalynchuk, 2006), the most plausible explanation appears to be a reciprocal relationship between stress promoting the development of mental disorders and psychiatric conditions being naturally accompanied by distress and a cortisol increase.

A limitation of this study is that clinical measures were not administered at the same time as the hair sample, although it was aimed to collect clinical data as close as possible. A possible explanation for the lack of association between cortisol and perceived stress and other measures is that they did not entirely correspond with the window of cortisol detection. Although the median time from clinical assessment to cortisol measurement was only 63.5 days, cortisol measurements corresponded approximately with the past 3 and 3 to 6 months, whereas some self-reported and interview measures captured information from the previous week or month only. This variability constitutes an issue concerning the reliability of correlations between cortisol and interview and self-report measures that were conducted for this study; however, the main finding of increased hair cortisol in the first segment in the clinical group is not affected since clinical participants experienced persistent distress at the time of hair sampling. The HC group did not receive clinical assessments, therefore were these clinical variables, functioning and lifestyle factors not included as covariates in the analyses. HC did not present with any threshold DSM disorder, however, it cannot fully be ruled out that sub-threshold distress disorders were present in this group. There was further a larger number of male participants in the clinical as compared to control group; however, this difference did not reach statistical significance.

Male sex and mixed-race ethnicity in women constituted a barrier in hair sample collection in terms of feasibility and refusal rates of this study, possibly creating a systematic

bias towards the findings. The clinical group included significantly more white individuals than the control group, whereas controls included more non-white (e.g. Asian and mixed-race) participants. Wosu et al. (2015) found differences in hair cortisol levels according to ethnicity, with lower levels in white participants. However, since our clinical group included more white participants, ethnicity is unlikely to account for the main finding of elevated hair cortisol. It is further unlikely that increased cortisol levels in the clinical group are due to antidepressant intake, as there were no differences in hair cortisol between those clinical participants who were taking antidepressant medication and those who were not.

A relatively small sample size is a further limitation, although as hypothesised, a group difference in hair cortisol concentrations in the first segment was discovered. Given the clinical heterogeneity of the sample, the sample size was not sufficient to conduct subgroup analyses (e.g. comparing different types of anxiety disorders). Differentiation of specific mental disorders on the basis of increases or decreases in cortisol (as seen in previous studies, e.g. for review, see Staufenbiel et al. (2013)) is more likely to happen where there is persistence and progression of symptoms, and therefore more probable to be distinguished over the future course of the illnesses in this population.

Lastly is to mention that it cannot be ruled out that recreational tobacco and alcohol consumption, as well as of other psychoactive illegal drugs, exerted effects. However, here was neither an association between hair cortisol and alcohol and tobacco use, nor an association with tobacco- and alcohol-related problems or behaviours. Parrott et al. (2014) found an almost 4-fold increase in hair cortisol levels in regular ecstasy users as compared to non-users. However, numbers were too small in the current sample to conduct meaningful analyses with any illegal psychoactive drugs.

The finding of elevated hair cortisol levels in young people with diverse mental health problems is consistent with increased HPA axis activity in the early stages of help-seeking for mental health problems. Future research should focus on disentangling how actual life stressors and subjective stress experience are associated with increases in cortisol and the

development and maintenance of mental disorders, and how HPA axis activity develops and

adapts over the course of illness and with remission of symptoms.

CHAPTER FIVE

BRAIN HYPO-ACTIVATION DURING WORKING MEMORY PERFORMANCE

Functional neuroimaging studies on working memory performance tend to segregate between a hyper-activation of certain brain areas in individuals with major depression (MD), as opposed to a hypo-activation in schizophrenia, most prominently reported in frontal areas such as the dorsolateral prefrontal cortex (PFC). Working memory performance was studied by means of an n-back (0- and 2-back) task in 34 young people (ages 16 – 26 years) with emerging mental health issues (10 males, M_{age} ± SD: 20.6 ± 2.5 years) and 34 age- and gender-matched HC (6 males, M_{age} ± SD: 20.4 ± 2.7 years). Further information was collected on clinical (e.g. depressive, psychotic, anxiety symptoms) and functional outcome, as well as longer-term cortisol levels. 2-minus-0-back-condition elicited activation of clusters mainly in the superior frontal gyrus (SFG), and in further frontal, parietal and subcortical regions in both groups (family-wise error (FWE)-corrected, $p < 0.05$). HC activated the left SFG, putamen, and anterior cingulate cortex (ACC), and right hippocampus and insula more strongly than clinical participants. There was no hyper-activation of any brain area in the clinical group. There were no differences in reaction times and accuracy between both groups, and no association with cortisol levels were detected (all $p > 0.05$). Adolescents and young adults with early mental health problems presented with brain hypo-activation, yet, with intact working memory performance. That is, subtle differences in brain activation are present during working memory, but do not yet translate into behavioural deficits in the clinical group. Longitudinal studies are required to track how these differences translate over time with illness progression and/or recovery.

5.1 Introduction

Working memory enables individuals to temporarily store and manipulate information that is necessary for understanding language, learning and reasoning (Baddeley, 1992). Working memory can be divided in executive control, which refers to encoding and retrieval of information, and actively maintaining information *on-line*. It has been proposed that the PFC holds control over executive processes, whereas the parietal cortex is engaged in active maintenance (Cohen et al., 1997). The finding of increased activation of the dorsolateral prefrontal, inferior and posterior frontal and posterior parietal cortex in early studies using a sequential letter memory task in healthy subjects (Cohen et al., 1997), has largely been confirmed by a more recent meta-analysis, with further activation being robustly identified in the premotor cortex, frontal pole and anterior cingulate (Owen et al., 2005).

A commonly employed variant to study key processes within working memory is the n-back task, which demands the monitoring of stimuli series. The participant has to indicate whenever a stimulus is presented as the one before *n* stimuli, where *n* could be 0, 1, 2, 3 etc. This involves monitoring, updating, and manipulating information that has previously been encoded and remembered, and requires working memory performance (Owen et al., 2005), with the task demand increasing with *n*. Likely functional roles during working memory, allocated to respective brain regions, are illustrated in Table 5.1.

Table 5.1

Likely functional roles for brain regions implicated in n-back task performance (Owen et al., 2005)

Brain region	Likely function
Dorsolateral prefrontal cortex	Mnemonic strategies: monitor series of stimuli, and compare every new stimuli with earlier one
Ventrolateral prefrontal cortex	Explicit intention to remember and retrieve information and sequencing of responses
Rostral prefrontal cortex & frontal pole	Problems comprising multiple cognitive processes (e.g. monitoring, adjustment and comparison of information)
Medial premotor cortex	Maintenance of attention, e.g. because of delay between stimulus and response
Anterior cingulate cortex	Response selection for goal-directed behaviours (Devinsky, Morrell, & Vogt, 1995)
Posterior parietal cortex	Spatial rehearsal

One mental disorder that has clearly been associated with working memory impairment and altered brain activation during those processes, is schizophrenia. Decreased working memory performance (Barch, Sheline, Csernansky, & Snyder, 2003; Lee & Park, 2005) and decreased activation in the dorsolateral prefrontal cortex (dlPFC) has been commonly reported (Barch et al., 2003), and referred to as *hypo-frontality* (Carter et al., 1998), and consistently coupled with increased anterior cingulate and left frontal pole activation (Barch et al., 2003). This pattern of hypo- and hyperactivation of rather distributed brain areas leads to view dlPFC dysfunction within the context of a network perspective, rather than focussing on an isolated dlPFC dysfunction, when aspiring to understand underlying mechanisms of schizophrenia (Glahn et al., 2005). Even though there are some studies that could not replicate decreases in dlPFC activation in schizophrenia patients (e.g. Manoach et al., 1999; Walter, Vasic, Höse, Spitzer, & Wolf, 2007), meta-analyses on executive functions (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009), and particularly on the n-back task (Glahn et al., 2005) in schizophrenia clearly supported the hypo-frontality hypothesis.

There is, however, inconsistent evidence concerning how brain activation during working memory is associated with the clinical presentation of schizophrenia: Whereas some studies did not detect correlations between symptom severity and reduced dlPFC brain activation in schizophrenia patients (Bleich-Cohen et al., 2014) and the severity of psychosis-spectrum symptoms and dlPFC activation in the general population (Wolf et al., 2015), found another one that decreased activation in frontal and parietal areas during a working memory task correlated with greater severity of negative and disorganisation symptoms (Sanz et al., 2009). This was further supported when looking at the effects of practice: Practising a working memory task reduced brain activation in the left dlPFC in both schizophrenia patients and controls, however, smaller effects were discovered in patients. This effect of practice on brain activation was – likewise - associated with severity of negative and disorganised symptoms (van Veelen, Vink, Ramsey, & Kahn, 2010).

Even though evidence is comparatively sparse, the literature indicates that affective disorders may also comprise abnormalities in fronto-subcortical networks using different brain imaging modalities (Soares & Mann, 1997). FMRI studies demonstrated inconsistent results with regards to executive function with studies indicating greater (Harvey et al., 2005; Matsuo et al., 2006), less, or no differences in activation when comparing depressed patients with HC (for review, see Rogers et al., 2004). Greater activation in patients was found, e.g. in the dlPFC and ACC in medicated (Harvey et al., 2005) and un-medicated patients (Matsuo et al., 2006). In the case of reports for hyper-activation, findings may be interpreted that cognitive capacity might be impaired in depressed patients and the same neural network needs to recruit more brain resources in those patients as compared to healthy individuals, in order to preserve a comparable working memory performance (Harvey et al., 2005). Hyper-activation of the cingulate cortex appears to sustain even with remission of depressive symptoms. With the dorsal anterior cingulate being crucial for cognitive and the ventral anterior cingulate being crucial for emotional processes, alterations in brain function are still abnormal even when patients' mood and other symptoms have improved (Schoening et al., 2009). This could reflect persistent changes in neuronal networks after a

MD episode or compensatory mechanisms to maintain performance (Schoening et al., 2009).

Considering the young age and early stage of mental health problems of the clinical participants in this study, as compared to the previously presented studies, it is conceivable that the latter present with far more pronounced changes in brain activation. Due to the lack of evidence of brain imaging studies in working memory in youth and early stage disorders, studies including healthy participants with a family history of schizophrenia and depression will be described, compared to which the current clinical participants are assumed to present with more pronounced changes in brain activation. Despite no behavioural differences in accuracy and reaction time, healthy siblings of schizophrenia patients showed a robust increased response of the right dlPFC, and bilateral inferior parietal lobule, and robust hypo-activation of the left medial frontal gyrus and left precuneus, PCC, thalamus and right hippocampus, compared to HC. This quantitative difference in brain activation implies that qualitative differences in information processing may exist in certain brain areas, without resulting in performance deficits (Callicott et al., 2003a). Similarly, an over-activation of diverse brain areas was observed in the offspring of depressed patients during a verbal working memory task. However, in that case, increased responses were observed in the lateral occipital, superior temporal and superior parietal cortex (Mannie, Harmer, Cowen, & Norbury, 2010). The presence of alterations of brain activation during working memory processes in healthy relatives of individuals with schizophrenia (Callicott et al., 2003a) and depression (Mannie et al., 2010), as well as the observation that deficits persist even after remission of depressive disorder for example (Schoening et al., 2009), indicate that these deficits might be a vulnerability marker for the respective disorders (Mannie et al., 2010).

Similarly to studies on healthy individuals with a family history of depression and schizophrenia, changes of brain activation in patients with depression did not translate into behavioural deficits: Actual working memory performance appears to be mostly intact in young to middle-aged depressed patients (Grant, Thase, & Sweeney, 2001; Harvey et al., 2005; Purcell, Maruff, Kyrios, & Pantelis, 1997), and only more severely impaired in older

hospitalised patients with chronic depressive conditions (Barch et al., 2003). Depression and age may have additive effects on executive functioning, and therefore leading to more distinct deficits (Snyder, 2013). A further factor that might contribute to executive functioning deficits is comorbidity. Some evidence suggests that anxiety disorders and trait anxiety are associated with executive functioning deficits, in a sense that co-occuring mental disorders may have an additive effect on respective impairments (Snyder, 2013). Taken together, performance deficits in working memory paradigms appear to be a function of severity of overall impairment, instead of being a distinct characteristic for any diagnostic category.

A variable that might moderate working memory performance and brain activation during these processes, is stress. Acute psychosocial stress was found to impair working memory performance in healthy males (Luethi, Meier, & Sandi, 2009), especially when cognitive load was high (Oei, Everaerd, Elzinga, Van Well, & Bermond, 2006). Glucocorticoid receptor agonists given to male rats into the medial PFC, led to an impairment of working memory (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010). This experimentally induced effect of decreased memory performance after glucocorticoid administration has been confirmed by human studies, when administration took place before memory retrieval (Het, Ramlow, & Wolf, 2005), and was further found to lead to decreases in hippocampal and PFC activation during declarative memory retrieval using fMRI (Oei et al., 2007). Experimentally induced psychological stress elicited reduced activity in the dlPFC and reduced deactivation of the PCC and orbitofrontal cortex (areas constituting the default-mode network) in healthy females during working memory processes (Qin, Hermans, van Marle, Luo, & Fernandez, 2009).

The aim of this study was to compare working memory performance and brain activation during a verbal n-back task between clinical participants with early mental health issues and HC. Further, brain activation of individuals scoring high on symptom score measures for psychotic, depressive and anxiety symptoms and psychological distress were compared with low symptom scores, and individuals with low social and role functioning were compared to high functioning individuals, and HC. Further covariates such as

antidepressant medication, chronic stress and working memory performance (accuracy) were considered for the fMRI analyses. Due to the young age and early stage and moderate severity of mental illness, no difference in performance between clinical participants and HC was hypothesised. Given the inconsistency of findings in terms of activation differences with hypo- and hyper-activation in psychotic and depressive patients or relatives of patients, e.g. of the dlPFC, and other cortical and subcortical areas, this study looked exploratively at potential activation differences as compared to HC in this very heterogeneous sample of young help-seeking clinical participants with diverse early mental health problems. Grouping into high symptom and low functioning was assumed to exacerbate brain activation when comparing to HC. Chronic stress was measured by means of hair samples, and hypothesised to correlate with activation of brain areas involved in working memory.

5.2 Methods

5.2.1 Participants

35 clinical participants who were experiencing psychological distress and 35 HC participated in this study. 1 clinical participant was excluded due to image distortion and 1 HC due to not pressing the correct button for the task. Both groups were recruited the same way as described in detail in Chapter 2 and Section 4.2.1. Exclusion criteria for both groups were a lack of sufficient English and cognitive ability to provide informed consent and adequately complete the assessments, neurological disorder, seizures, or significant head injury and any contraindications for MRI. Participants had normal or corrected-to-normal vision and hearing. HC were age, gender, occupation and education matched, and required to have no personal (assessed using the Structured Clinical Interview for DSM disorders screen and report ("SCID", American Psychiatric Association, 2000)) or first-degree family history of mental illness. The study was approved by the local ethics committee and participants gave their informed consent.

5.2.2 Measures

Demographic information covered participants' age, gender, ethnicity, occupation and highest qualification. Handedness was enquired via self-report as potential confounder for the MRI. Use of psychiatric medication such as antidepressants, neuroleptics, beta-blockers, anticonvulsants in the past 6 months was gathered. Interview and self-report measures from the baseline clinical assessment were used, with median time from the first clinical assessment to scanning being 63.5 days (range 5 - 199 days).

The CAARMS, and SOFAS were employed to determine UHR status, the presence of PLE and threshold psychosis (as described in Section 2.5). QIDS, OASIS, K-10, and Social and Role scale were further utilised to compare brain activation of clinical participants with high and low symptom scores and high and low functioning, with the respective other group of clinical participants and HC. Cut-offs and classifications are illustrated in Table 5.2.

Table 5.2
Cut-offs for clinical measures and functioning for brain activation comparisons

	High scores	Low scores
CAARMS	Psychotic (n=3) UHR (n=6) PLE (n=8)	No significant psychotic symptoms (n=17)
QIDS	Moderate to severe depressive symptoms (Score ≥11) (n=19)	None to mild depressive symptoms (Score <11) (n=15)
OASIS	Anxiety diagnosis (Score ≥8) (n=24)	No anxiety diagnosis (Score <8) (n=10)
K-10	Severe mental disorder (Score ≥30) (n=20)	Up to moderate mental disorder (Score <30) (n=13)
Social Functioning	Moderate impairment to superior functioning (Score 6-10) (n=21)	Serious impairment to extreme dysfunction (Score 1-5) (n=13)
Role Functioning	Moderate impairment to superior functioning (Score 6-10) (n=19)	Serious impairment to extreme dysfunction (Score 1-5) (n=15)

Notes. CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory of Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K10=Kessler Psychological Distress Scale, UHR=ultra-high risk, PLE=psychotic-like symptoms.

Perceived stress and cortisol levels

Perceived stress (as measured with the PSS (Cohen et al., 1983) (for the past month) and chronic cortisol levels (for the past 3 months) were determined via scalp hair samples (for detailed information, see Section 4.2).

5.2.3 Imaging

5.2.3.1 Task

Participants underwent one run of a 6 minutes fMRI scan including the 0 and 2-back version of a verbal n-back task, being presented with sequences of letters in the centre of the screen. In the 0-back condition participants were required to indicate with the index finger of their dominant hand, whenever the letter "X" appeared. During the 2-back condition, the task was to similarly press the same button, however, when participants saw a letter that was the same as the one before last presented. Each of those blocks lasted for 24 seconds, and every two blocks were separated by 38 seconds of rest. The block order was the following: 0 - 2, rest, 0 - 2, rest, 2 - 0, rest, 2 - 0, rest. During rest conditions a fixation cross

was presented in the centre of the screen, followed by two fixation crosses, indicating the beginning of the next block/the end of the task. Within each block 12 letters were shown, each for 2 seconds, with 3 of each block being targets (see Figure 5.1). The memory condition (2-back) was contrasted with the 0-back as sensori-motor and attentional control condition (Glahn et al., 2005). In total, 169 whole-brain fMRI volumes were obtained. High- and low-performing clinical participants were determined by using a median-split of accuracy in the 2-back condition for the whole sample (median = 0.955) and for cortisol covariance analyses (median = 10.98pg/mg) and compared with HC.
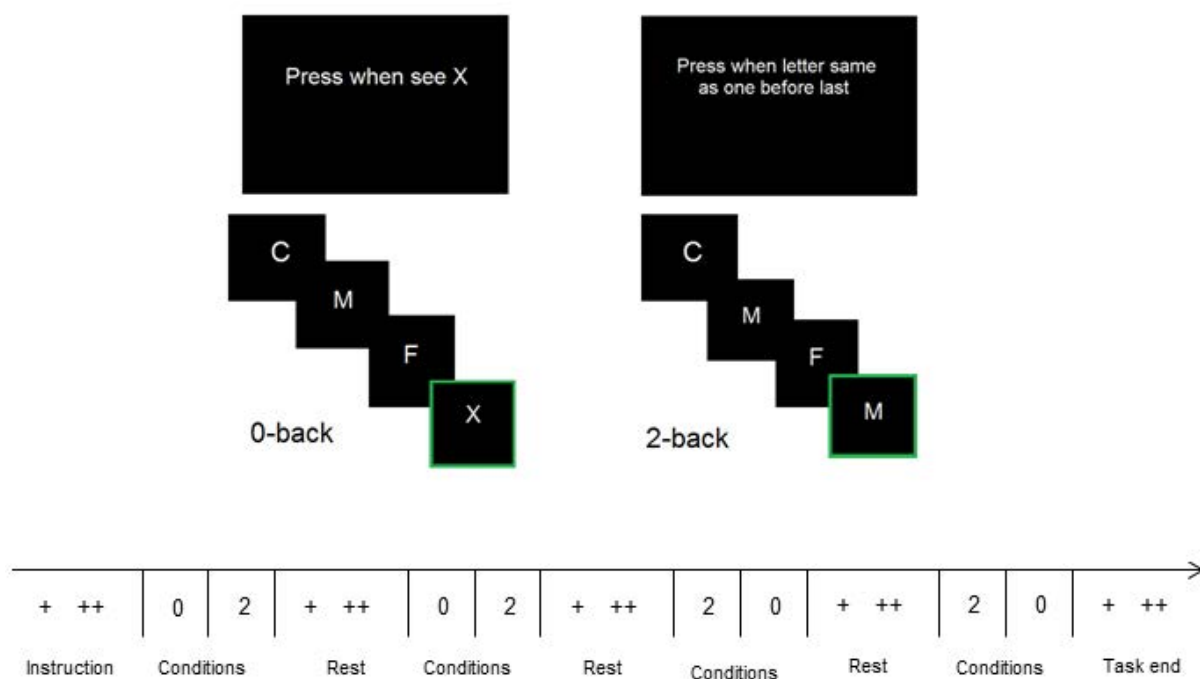
Figure 5.1. Experimental design of n-back working memory task.

The n-back paradigm was chosen as working memory paradigm as it enables to synthesise and compare results across different studies and populations (Owen et al., 2005), and a 2-back condition was chosen as memory condition to evoke sufficient activation of

resources, but without compromising the validity of results by employing a too difficult task, so that the ability to successfully perform would decrease (Callicott et al., 1999).

5.2.3.2 Data acquisition

The study was conducted at the Birmingham University Imaging Centre using a 3T Philips Achieva MR scanner for obtaining fMRI (169 dynamics, ascending order, TE = 35 msec, whole-brain coverage, TR = 2.2 seconds, voxel size 2.5 x 2.5 x 3 mm) and high-resolution 3D T1-weighted MRI data using a 32-channel head coil. T1-weighted images (TR = 8.4 msec, TE = 3.8 msec, flip angle = 8°, FOV = 288 x 232 x 175 mm, voxel size 1 x 1 x 1 mm) were co-registered to the fMRI data for localisation.

5.2.3.3 Data analysis

Behavioural data was analysed using E-Prime Professional 2.0 (Schneider & Zuccoloto, 2007). MRI scans were automatically processed with statistical parametric mapping software (SPM8, Friston, The Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

Functional scans were realigned with the middle scan as a reference. Motion was corrected using ArtRepair (http://spnl.stanford.edu/tools/ArtRepair/ArtRepair.htm) in SPM8, if rotations were more than 2 degrees or translations more than 2.5 mm. Algorithms of this software reduce residual errors by automatically detecting and removing noisy volumes, slices, trends, and voxel-wise spikes in the data (Mazaika, Hoeft, Gover, & Reiss, 2009). Images were normalised using Montreal Neurological Institute (MNI) templates (Talairach & Tournoux, 1988) and smoothed with a 5 × 5 × 6 mm full width at half maximum (FWHM) Gaussian kernel. First-level analyses included modelling of blood-oxygenation level-dependent (BOLD) signal changes of the 2- and 0-back condition individually for all participants. Motion parameters were included as regressors in each individual's first level analysis.

The statistical parametric maps from each individual from both clinical participants and HC were then compared using independent samples t-test at the second level. ANOVA were used when splitting clinical participants into high and low symptom, functioning, and accuracy scores and comparing the resulting two groups with HC. Additional regression analyses were conducted in the clinical group to see if clinical and functioning measures positively or negatively correlated with brain activation, in order to determine whether a dimensional perspective using total scores, contributes to understanding changes in brain activation during working memory. ANCOVA were employed for determining the potential effect of cortisol and perceived stress levels on brain activation when comparing clinical participants (n = 26) with HC (n = 26). Individual maps for clinical participant and control group and group comparisons were contrasted for *2-minus-0-back* condition. Only clusters with a size greater than 10 contiguous voxels were reported. Voxel-wise statistical analysis was employed with threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) and FWE-correction for multiple comparisons for all analyses thresholded at $p < 0.05$. TFCE was employed which optimises areas of signal that show spatial contiguity without being reliant upon hard threshold-based clustering. An algorithm runs though the image, with the aim to better distinguish between signal and noise (Smith & Nichols, 2009).

Demographic information, and accuracy and reaction time of the n-back task was compared for clinical participants and HC, using t-, U- and x^2-tests. Spearman correlations were conducted to investigate the association between n-back task performance and cortisol and perceived stress levels.

5.3 Results

5.3.1 Demographic, behavioural and clinical data

Clinical participants and HC did not differ in terms of age, gender, handedness, occupation and highest qualification, however, the majority of the clinical sample was White-British, whereas HC were more mixed in terms of ethnicity (see Table 5.3). The time from clinical baseline assessment to the scan date ranged from 5-199 days, with a median time of 63.5 days.

Table 5.3
Demographic information on clinical participants and HC

	Clinical participants (n=34)	HC (n=34)	Test statistic	p-value
Mean age ± SD *(in years)*	20.6±2.5	20.4±2.7	$t(66)=0.29$	0.78
Range	16-25	16-25		
Gender (m/f)	10/24	6/28	$X^2(1)=1.31$	0.25
Handedness (right/left)	28/6	31/3	$X^2(1)=1.15$	0.28
Ethnicity				
White[1]	28	18		
Asian[2]	1	7	$X^2(3)=7.84$	0.05*
Black[3]	2	4		
Mixed-race[4]	3	5		
Occupation				
University student[5]	10	17		
College/A-Levels	11	6	$X^2(4)=7.17$	0.13
Unemployed	5	2		
Employed[6]	6	9		
Homemaker	2	0		
Highest qualification				
University[7]	4	9		
A-Levels[8]	16	19	$X^2(3)=5.76$	0.12
GSCE[9]	13	6		
No qualification	1	0		
Psychiatric medication				
Antidepressants	18	0	$X^2(1)=26.25$	<0.001***
Neuroleptics	1	0	$X^2(1)=0.98$	0.32
Beta-blockers	1	0	$X^2(1)=0.98$	0.32
Anticonvulsants	1	0	$X^2(1)=0.98$	0.32
Performance on n-back task				
0-back (Median % correct; range)	100; 0.04	100; 0.02	U=475.5, Z=-2.25	0.02*
2-back (Median % correct; range)	96; 0.22	97; 0.17	U=497, Z=-1.02	0.31
Overall n-back (Median % correct; range)	98; 0.11	99; 0.07	U=471.5,Z=-1.34	0.18
0-back RT (Median, in msec; range)	473; 370	444; 299	U=510,Z=-0.83	0.4
2-back RT (M±SD, in msec)	619±117	617±129	$t(66)=0.07$	0.95
Overall n-back RT (M±SD, in msec)	540±86	528±82	$t(66)=0.65$	0.58

Notes. HC=healthy controls, M=mean, SD=standard deviation, m=male, f=female, RT=reaction time.
[1] White-British & White-Other, [2] Asian-Pakistani, Asian-Bangladeshi & Other Asian, [3] Black-African, [4] Mixed-Race White-Black-Caribbean, [5] Undergraduate and postgraduate university students, [6] Working full or part-time, [7] Bachelor or Master degree, [8] A-Levels, National Vocational Qualification (NVQ) Level 4, or equivalent, [9] General Certificate of Secondary Education (GCSE, year-10 equivalent) or NVQ level 1 or 2, * p < 0.05, *** p < 0.001.

There were no significant differences in 0- and 2-back reaction time and accuracy between clinical participants and HC (all $p > 0.05$), apart from a not meaningful statistically significant difference in median reaction time for the 0-back condition (see Table 5.3). Accuracy in the n-back task was significantly worse for the 2-back as compared to 0-back condition for the whole sample ($Z = -6.11$, $p < 0.001$), and for both clinical participants ($Z = -4.37$, $p < 0.001$) and HC ($Z = -4.3$, $p < 0.001$). Across the overall sample, males responded faster in the 2-back ($t (66) = -2.53$. $p = 0.01$) and overall n-back condition ($t (66) = -2.21$, $p = 0.03$), however there was no group x gender interaction ($p > 0.05$). No further measures of n-back performance were correlated with gender, age and highest qualification.

Clinical participants were on average moderately depressed (QIDS), had an anxiety diagnosis (OASIS) and were in general classified as having a severe mental disorder (K-10). Three individuals were classified as psychotic, 6 as UHR for psychosis, 8 as having PLE and 17 as having no significant psychotic symptoms according to the CAARMS. Social functioning was on average moderately and role functioning on average seriously impaired (see Table 5.4). Neither one of the clinical measures was associated with n-back accuracy and reaction time (all $p > 0.05$).

Table 5.4
Clinical measures (n=34)

Measure	Range	M±SD
CAARMS	0-33	14.4±8.8
QIDS	3-19	11.1±4.3
OASIS	0-19	9.7±4.4
K-10 (n=33)	18-49	31.4±7.3
Social Functioning	3-9	6.1±1.7
Role functioning	1-9	5.2±2.6

Notes. CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory of Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K-10=Kessler Psychological Distress Scale.

5.3.2 fMRI data

5.3.2.1 Working memory activation in clinical participants and HC

2-0 back condition mainly activated a cluster in the SFG in HC and clinical

participants, and further clusters in the supramarginal gyrus (SMG), ACC, caudate nucleus

and cerebellum in HC, and in the middle frontal gyrus and orbitofrontal cortex in clinical

participants (p < 0.05, FWE-corrected) (see Figure 5.2/Table 5.5).
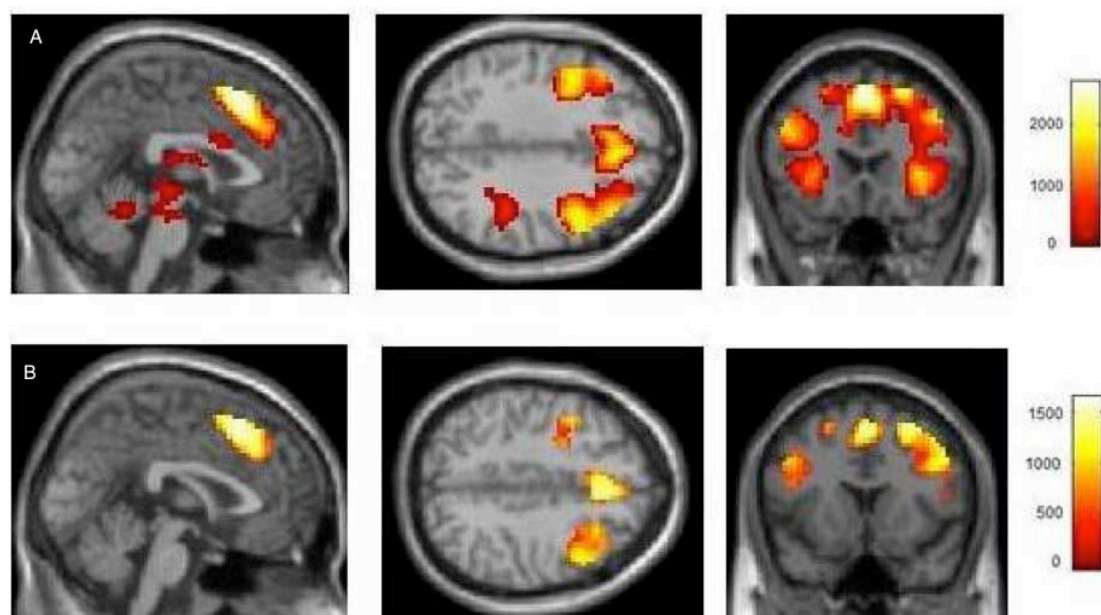
Figure 5.2. Activation pattern of 2-0 back in (A) HC and (B) clinical participants (FWE-corrected p<0.05).

Table 5.5
Brain areas, coordinates and statistics for 2-0 back activation
for clinical participants and HC (*FWE-corrected p<0.05)*

Brain area	MNI coordinates	TFCE cluster	P
HC			
Superior frontal gyrus	3 20 49	5794	<0.001***
Supramarginal gyrus	45 -37 43	1829	<0.001***
Anterior Cingulate Cortex	-3 8 25	5740	0.002**
Caudate nucleus	-15 2 13	1136	0.001**
Cerebellum	0 -52 -20	423	0.022*
Clinical participants			
Superior frontal gyrus	3 20 49	1651	<0.001***
Middle frontal gyrus	27 5 55	1491	<0.001***
	-42 23 28	1116	0.002**
Orbitofrontal gyrus	33 26 -2	1024	0.003**

Notes. HC=healthy controls, FWE=family-wise error-corrected, MNI=
Montreal Neurological Institute, TFCE=threshold-free cluster enhancement,
* p < 0.05, ** p < 0.01, *** p < 0.001.

The left SFG (k = 545, -12 29 40, p = 0.002 FWE-corrected), hippocampus (k = 314, 21 -34 13, p = 0.031 FWE-corrected & k = 300, 24 -37 10, p = 0.038 FWE-corrected), putamen (k = 307, -30 -16 -8, p = 0.035 FWE-corrected), ACC (k = 302, -9 41 13, p = 0.037 FWE-corrected) and insula (k = 301, 27 -28 19 FWE-corrected) showed less activation in clinical participants with mental health issues as compared to HC (see Figure 5.3). There was no pattern of hyper-activation in clinical participants compared to HC during working memory (FWE-corrected p < 0.05).
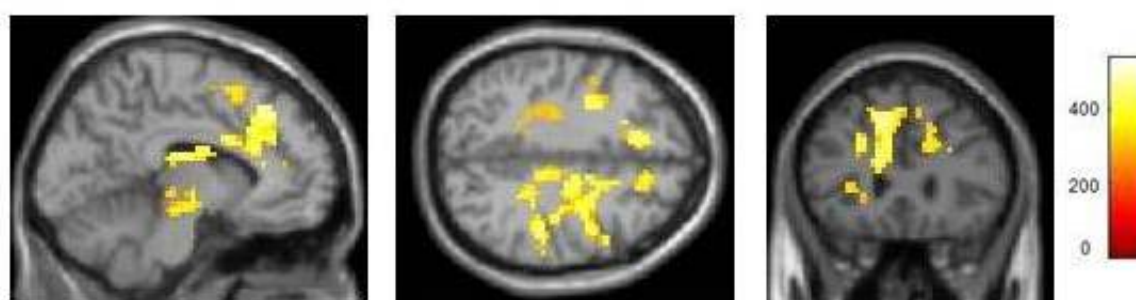
Figure 5.3. Hypo-activation pattern in clinical participants (FWE-corrected p<0.05).

5.3.2.2 Working memory activation, clinical measures and other covariates

In order to observe if changes in brain activation are potentially moderated by severity of symptoms or impairment of functioning, clinical participants with high levels of clinical symptoms or low levels of functioning (as outlined in Table 5.2) were compared with the respective other clinical participant group and also HC using ANOVA with 6 contrasts ("HC minus high score", "HC minus low score", "high score minus HC", "low score minus HC", "high score minus low score", "low score minus high score"). Only the contrasts "HC minus high score" and "HC minus low score" yielded significant results (FWE-corrected, p < 0.05) as follows: Hypo-activation was observed for individuals with high depressive, psychotic, and anxiety symptoms and high general distress, low social and role functioning, and low psychotic symptoms and high social functioning when respectively compared to HC. Coordinates, labels for hypo-activated brain areas, cluster sizes and significance levels of the respective groupings of clinical participants as compared to HC, are illustrated in Table 5.6.

Table 5.6

Brain areas, coordinates and statistics of hypo-activation when comparing high/low symptomatic and high/low functioning clinical participants with HC for 2-0 back activation (FWE-corrected p<0.05)

Brain area	MNI coordinates	Cluster size	P
High depressive symptoms vs HC			
Superior frontal gyrus	-12 29 40	566	0.004**
Precentral gyrus	51 8 28	327	0.043*
Orbitofrontal cortex	-36 26 -8	326	0.043*
Supramarginal gyrus	-27 -40 37	325	0.044*
Thalamus	-24 29 -2	319	0.045*
Putamen	33 -4 -8	319	0.045*
Caudate nucleus	-15 8 19	319	0.045*
High psychotic symptoms vs HC			
Superior frontal gyrus	24 -1 40	575	0.004**
Hippocampus	36 -10 -14	333	0.032*
Caudate nucleus	-21 23 7	323	0.036*
Low psychotic symptoms vs HC			
Postcentral gyrus	39 -22 34	287	0.037*
Middle temporal gyrus	39 -28 -5	273	0.044*
Anterior cingulate cortex	6 8 25	267	0.047*
High anxiety symptoms vs HC			
Superior frontal gyrus	-12 29 43	623	0.001**
Temporal lobe	42 -40 -8	335	0.027*
	21 -34 13	305	0.039*
Precentral gyrus	-24 -22 49	299	0.040*
Insular cortex	33 8 -5	378	0.023*
Posterior cingulate cortex	9 -37 43	293	0.044*
Anterior cingulate cortex	-9 41 13	292	0.044*
	-12 38 16	290	0.046*
Premotor cortex	-15 -16 52	285	0.048*
Parahippocampal gyrus	21 -34 -5	285	0.049*
High general distress vs HC			
Superior frontal gyrus	-12 26 43	680	<0.001***
Insula	33 8 -5	327	0.03*
Temporal lobe	42 -40 -8	325	0.031*
Thalamus	18 -22 -2	316	0.035*
Caudate nucleus	15 2 22	310	0.037*
Precentral gyrus	-24 -22 49	306	0.038*
Posterior cingulate cortex	9 -28 34	298	0.043*
	-15 -37 34	296	0.044*
Low role functioning vs HC			
Superior frontal gyrus	-12 26 40	591	0.005**
Insula	-33 5 -11	356	0.030*
Caudate nucleus	9 11 16	345	0.033*
Paracingulate gyrus	18 44 1	329	0.039*
Insula	-36 -4 7	316	0.044*
Posterior cingulate cortex	-12 -13 34	302	0.049*
Low social functioning vs HC			
Brainstem	-6 -25 -11	386	0.019*
Anterior cingulate cortex	-6 5 28	371	0.021*
	-15 29 16	305	0.047*
	-15 20 28	301	0.05

Superior frontal gyrus	-12 29 40	352	0.026*
Caudate nucleus	-18 5 25	324	0.035*
	-12 -4 22	306	0.047*
Middle temporal gyrus	51 -46 -5	321	0.037*
Putamen	-33 -16 -8	315	0.042*
Inferior temporal gyrus	39 -52 -2	312	0.043*
Insula	-33 -34 4	309	0.046*
Posterior cingulate cortex	9 -31 37	303	0.049*
Paracingulate gyrus	-12 23 25	301	0.05
Occipital cortex	39 -61 -8	301	0.05
High social functioning vs HC			
Paracingulate gyrus	-12 26 40	379	0.013*
Precentral gyrus	51 8 25	374	0.015*
Somatosensory cortex	-39 -7 28	319	0.027*
Thalamus	12 -19 16	297	0.036*
	18 -22 -2	297	0.037*
	9 -22 -2	280	0.045*
Anterior cingulate cortex	-6 20 19	291	0.039*
Posterior cingulate cortex	6 -34 19	285	0.042*
Insula	33 14 -2	285	0.043*

Notes. HC=healthy controls, FWE=family-wise error-corrected, MNI=Montreal Neurological Institute, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Further regression analyses with total scores of the CAARMS, QIDS, OASIS, social and role functioning (n = 34), and K-10 (n = 33) did not reveal positive or negative correlations with brain activation during working memory performance. When clinical participants were split into high (n = 17) and low-performing (n = 17) individuals according to their accuracy in the working memory (2-back) condition and compared to HC, using an ANOVA, only a hypo-activation in the low-performing group as compared to HC was evident in the ACC (k = 739, 6 5 25, p = 0.002 FWE-corrected), SFG (k = 368, k = 368, 21 -4 49, p = 0.034 FWE-corrected), Heschl's gyrus (k = 334, 45 -19 7, 0.047 FWE-corrected & k = 334, 48 -22 4, p = 0.047 FWE-corrected), and precentral gyrus (k = 329, 15 -10 55, p = 0.049 FWE-corrected). Clinical participants who were taking antidepressants demonstrated no different brain activation as compared to clinical participants without antidepressant medication (FWE-corrected, all p > 0.05).

5.3.2.3 Brain activation, task performance, cortisol, and perceived stress levels
There was a negative association between accuracy in the 2-back and overall n-back condition with cortisol levels and with perceived stress levels (see Table 5.7). Neither a

association between 0-back condition and cortisol or with perceived stress levels was

observed, nor a correlation between reaction time and both of the investigated stress

parameters.

Table 5.7
*Spearman correlations between task accuracy
and cortisol and perceived stress levels (n=52)*

Brain area	r_S	P
Cortisol		
2-back accuracy	-0.301	0.030*
overall n-back accuracy	-0.309	0.026*
Perceived Stress		
2- back accuracy	-0.276	0.048*
overall n-back accuracy	-0.313	0.024*

Notes. * $p < 0.05$.
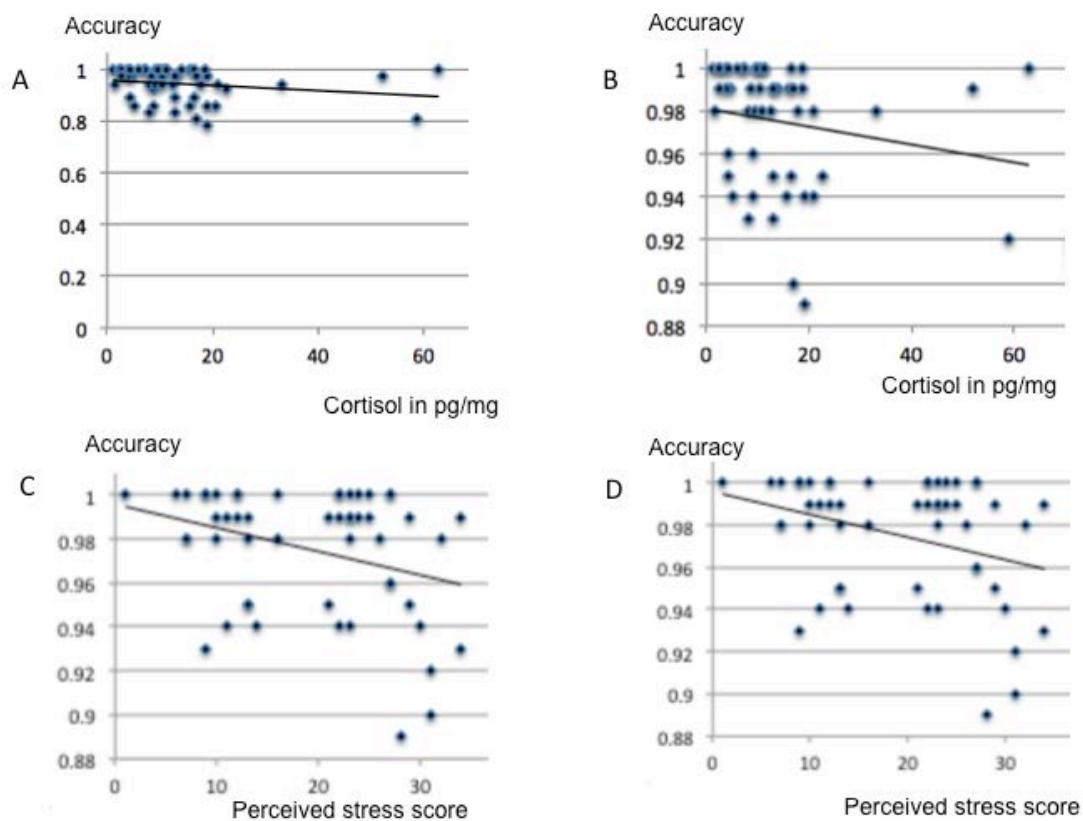
Figure 5.4. Correlations between (A) hair cortisol and 2-back task accuracy, (B) hair cortisol and overall n-back task accuracy, (C) perceived stress score and 2-back task accuracy, and (D) perceived stress score and overall n-back task accuracy.

No areas in the brain correlated with increased or decreased activation and cortisol or perceived stress levels when correlating cortisol and perceived stress with brain activation in clinical participants and HC individually, and when comparing clinical participants with HC using ANCOVA (all $p > 0.05$, FWE-corrected). Due to the correlation between accuracy and cortisol levels, clinical participants were classified into high- (n =14) vs low- (n = 12) performing, and compared with HC using a three-group ANCOVA. However, likewise no brain areas correlated with cortisol in this analysis (all $p > 0.05$, FWE-corrected).

5.4 Discussion

This study looked at differences between young people with early mental health problems and HC in brain activation during working memory performance, the association of brain activation with clinical symptoms, functioning, hair cortisol levels and indices of task performance. The n-back task activated mainly frontal, but also parietal and marginally subcortical brain regions in HC and clinical participants in the superior and middle frontal gyrus, and SMG, ACC, orbitofrontal cortex and basal ganglia, overlapping or closely adjacent to those areas typically detected as relevant for a verbal working-memory task in previous literature, such as the dlPFC, and posterior parietal cortex (Owen et al., 2005). Clinical participants with mental health issues showed a reduced response in the SFG, ACC, insula, putamen and hippocampus, however, no hyper-activation was detected in clinical participants. Comparing clinical participants with high symptom and low functioning scores to HC replicated the finding of hypo-activation, however of rather distributed brain areas. No meaningful behavioural group differences in reaction time and accuracy, and no associations with cortisol, and perceived stress levels, and with dimensional scores of the respective clinical and functioning measures were detected.

The finding of intact behavioural working memory performance is in agreement with previous literature in young to middle aged depressed patients (Grant et al., 2001; Harvey et al., 2005; Purcell et al., 1997). Even though abnormalities in BOLD signal, especially in frontal areas such as the dlPFC, were usually identified in studies investigating schizophrenia (Barch et al., 2003; Glahn et al., 2005), depression (Harvey et al., 2005; Matsuo et al., 2006) and family history of these disorders (Callicott et al., 2003a), it is yet not fully clear why some report decreases and other increases (Callicott et al., 2003a). One possible explanation is coming from a study dividing schizophrenia patients into high- and low-performing individuals. Patients who sustained a comparable performance to HC, showed greater prefrontal activation, whereas patients who achieved lower accuracy, showed decreased prefrontal activation (Callicott et al., 2003b). The current study found

decreases in frontal brain activation when behavioural performance was intact. Alterations of brain function during working memory processes appear to emerge during these early stages of mental problems, but with the task encompassing moderate cognitive load, these differences might not yet translate into behavioural deficits.

With task difficulty being a factor that has an important effect on the strength and extent of the BOLD response, more difficult conditions might have been associated with greater brain activation than easy conditions (Fu et al., 2002), and behavioural impairments may have therefore only become visible when cognitive load is high (Callicott et al., 1999; Walsh et al., 2007), together with further or more pronounced alterations in clinical participants' brain activation. The 2-back condition that was used, may have been too easy to elicit more distinct differences between groups, given the young age and comparatively high educational level of both clinical participants and HC. This notion is further supported by finding a ceiling effect in both groups in accuracy and reaction time. However, the current sample consisted of adolescents and young adult outpatients. Only 3 of the clinical participants were experiencing a psychotic episode according to the CAARMS at some point in the past year, and depressive symptoms existed on a moderate level. This is opposed to other studies that often looked into established disorders of inpatients with multiple recurrences of episodes, a more extended length and more pronounced severity of illness, and it therefore may simply be that working memory performance is still intact in the current sample.

When high-symptomatic and low-functioning clinical participants were compared to low-symptomatic and high-functioning clinical participants, no difference in brain activation was discovered, however, generally high-symptomatic and low-functioning clinical participants demonstrated hypo-activation of diverse and distributed frontal, parietal, temporal, insular, cingulate and subcortical brain areas as compared to HC. This demonstrates the robustness of the finding of hypo-activation during working memory processes, but also that symptom severity of some clinical measures might moderate this effect. Clinical participants scoring high on depressive, and anxiety symptoms, psychological distress and low on role

functioning showed brain hypo-activation as compared to HC, whereas this difference was not evident for psychotic symptoms and social functioning, where both clinical participant groups displayed deviant brain activation as compared to HC. One possible explanation for this finding is that the cut-offs used for these two clinical measures are not relevant for differentiating brain activation during working memory processes in this early stage of disorder. Regression analyses of clinical and functioning scores of the clinical group did not reveal correlations with brain activation. Even though symptom severity is considered to be relevant for brain activation as demonstrated when splitting clinical participants into high and low symptom and functioning scores, this finding could not be replicated when using a rather dimensional approach. This could possibly be due to the reduced power of the latter analyses with only including clinical participants instead of the whole sample, or is an expression of a problem with approaching this from a dimensional perspective.

The finding of no differences in brain activation between clinical participants taking antidepressants and those who were not, is consistent with the observation that some differences persist even with remission of symptoms (Schoening et al., 2009), even though this study did not discover activation differences in the cingulate between clinical participants and HC. It further confirms that antidepressant treatment may not particularly be affecting the neural circuits involved in working memory.

Cortisol and perceived stress levels were negatively associated with working memory accuracy across the whole sample. As opposed to the hypotheses, no correlation between chronic stress levels, as measured by hair cortisol and perceived stress, and brain activation in the working memory network was confirmed. This may be due to the fact that previous studies looked into the *acute* effects of psychosocial stress (Lueti et al., 2009; Oei et al., 2006) or glucocorticoid administration (Het et al., 2005) in healthy individuals, whereas the current study explored and compared *chronic* stress of mentally ill patients with HC. Clinical participants showed significantly increased cortisol levels as well as perceived stress (see Section 4.3), however, this may involve different pathways in the brain than acutely increased cortisol levels, and/or only show with persistence of illness or illness progression.

There are certain limitations to the study that have to be acknowledged. Firstly, the conduction of multiple comparisons has to be acknowledged. Even though stringent FWE-correction was used for within-analysis comparisons on the voxel-level, multiple comparisons were conducted for dividing the clinical group into high vs low scores for clinical and functioning measures, performance, and hair cortisol levels, each consisting of six contrasts, respectively. However, this distinction of the clinical group replicated the finding of brain hypo-activation of the generally more impaired clinical participants as compared to HC. Secondly, there is a large number of potential confounders while scanning, e.g. the level of experienced anxiety and arousal (Paus et al., 2008) during the fMRI session that may influence task performance and brain activation, as well as head motion, whereas motion parameters were included as covariate of no interest in the analyses and excessive head motion was corrected using specialised software. Albeit mild to moderate claustrophobia tendencies were observed for both clinical participants and HC (see Appendix B-18, MRI safety screening questionnaire, question "Are you claustrophobic?"), no proper measure was used that could give further insight into this issue. Similarly, as outlined in Section 4.4, the time elapsed between clinical assessments and brain scan is an issue for the interpretation of fMRI data that involves ANOVA and regression analyses with interview and self-report data, as both imaging and clinical data contains highly state-specific information which in most cases has been collected on different assessment dates. Further, no measure of general intelligence or socio-economic status was employed that could help to gain insight into pre-existing group differences, however, no differences in highest qualification or employment status were detected that indicate that the observed decreased brain activation in clinical participants might be due to these covariates. As opposed to other, less controlled studies, the current investigation included HC only if they had no family or personal history of any mental disorders that may be associated with abnormal brain activation. This is of particular relevance since family history, e.g. of schizophrenia (Callicott et al., 2003a) or depression (Mannie et al., 2010) was found to be associated with abnormal brain activation during working memory.

Together, there was a hypo-activation, mainly of frontal areas and the thalamus and brainstem in individuals with early mental health issues as compared to HC. Symptom and functioning scores moderated this finding, however, no behavioural differences and no association with cortisol levels were observed. The current sample was characterised by a young age and comparatively short duration of illness, and predominantly mild to moderate symptom severity concerning depressive, psychotic and anxiety symptoms. Longitudinal investigation of the sample might help to disentangle whether age, recurrence of episodes, length and severity of illness, and comorbidity are associated with more pronounced disturbances in working memory in mental illnesses such as psychosis and depression.

CHAPTER SIX

SUBTLY REDUCED CONNECTIVITY OF BRAIN NETWORKS DURING REST

Resting-state functional magnetic resonance imaging (rs-fMRI) has revealed connectivity alterations in MD, anxiety, and schizophrenia as well as in at-risk individuals, in large-scale brain networks such as the default-mode and salience network. The aim of the present study was to investigate functional connectivity of brain networks in a group of young, help-seeking individuals with mental health problems. 32 young individuals with mental health issues and 32 HC underwent a 10-minute rs-fMRI scan. ICA was employed with independent components being estimated using a single group ICA with all 64 individuals. A dual regression method was used to create individual representations of the networks. Voxel-wise permutation tests were conducted to compare spatial maps of both groups ($p < 0.05$, FWE-corrected). ICA isolated the default-mode, salience, the dlPFC as part of the executive-control network, the primary, medial and lateral visual, auditory, sensori-motor, ventral stream and left and right fronto-parietal network. The auditory and somatosensory network displayed significantly reduced resting-state connectivity in the SMG, and a trend for reduced connectivity in the PCC. Clinical participants with (sub-) threshold psychotic symptoms, and with moderate to severe depressive symptoms showed significantly reduced connectivity in networks such as the auditory and somatosensory network, and ventral stream as compared to HC. The ICA replicated commonly found resting-state brain networks in young individuals with early mental health problems and HC. Functional resting-state connectivity in the whole clinical group was largely intact, and more pronounced network alterations became only apparent when considering symptom severity. Longitudinal studies with larger samples are needed to illuminate altered functional connectivity in specific networks in the course of illness.

6.1 Introduction

The human brain is a complex organisation of structurally and functionally inter-connected areas. Large-scale brain networks constitute an integrative model of how disturbances of brain connectivity are associated with cognitive and affective dysfunction in psychiatric disorders (Menon, 2011). Brain connectivity of various mental disorders has been investigated on the grounds of this - on the forefront of these investigations schizophrenia has been proposed to involve brain dysconnectivity, especially of frontal areas (Pettersson-Yeo et al., 2011). Deficits in the maintenance of these neurocognitive networks in other disorders such as depression and anxiety has been demonstrated as well (Menon, 2011). Depression, e.g. involves various symptoms domains (such as mood, cognition, etc.), and these domains can manifest at opposing ends of one and the same symptom category (e.g. hyper- vs hyposomnia). Therefore it is rather unlikely that the heterogeneity of depressive symptomatology can by explained by alterations of individual brain areas (Veer et al., 2010), but instead by dysregulation of multiple areas of brain circuits, amongst others including the PFC, ACC, amygdala, and hippocampus (Davidson, Pizzagalli, Nitschke, & Putnam, 2002).

The large-scale networks of most interest in psychiatric disorders are the salience (SN), default-mode (DMN), and executive control network (ECN). The SN is anchored in the dorsal anterior cingulate and fronto-insular cortices; the DMN consists of the PCC, medial PFC, medial temporal lobe, and angular gyrus; and the ECN is a fronto-parietal system anchored in the posterior parietal cortex and dlPFC (Menon, 2011). These large-scale networks typically appear to be distinguished on the basis of whether they are up- or down-regulated during specific cognitive tasks, and hence described as either *task-positive* (being activated during tasks) or *task-negative* (being de-activated during tasks, and activated during rest), such as in the case of the DMN (Cole, Smith, & Beckmann, 2010; Fox et al., 2005). The SN usually switches between the DMN and ECN to guide behaviour, e.g. to enable access to attention and working memory resources when needed (Menon & Uddin, 2010).

Some functional brain networks are formed before the onset of puberty, but the structure and connectivity within these networks may be altered throughout adolescence (Stevens, Pearlson, & Calhoun, 2009). Stevens et al. (2009) found fewer significant connections between networks and increases of functional integration strength within networks with increasing age in healthy individuals aged 12 to 30 years. The DMN was found to be sparsely connected in 7-9 year old children, whereas over time these brain areas connected to a cohesive network in adulthood (Fair et al., 2008). Furthermore, the fronto-parietal network strengthens its connections with age (Fair et al., 2007). A review on functional brain networks (Uddin, Supekar, & Menon, 2010) summarised that brain activation during cognitive tasks tends to progress from diffuse activation to an increase of the magnitude of activation of key frontal brain areas with increasing age, constituting more efficient processing. A developmental over-connectivity which is followed by pruning is hypothesised to help the reorganisation of (sub-)cortical connectivity. Furthermore, it was reported that demands on the PFC decrease, with shifting demands on posterior regions, and that connectivity within local functional circuits of one hemisphere preceeds inter-hemispheric connectivity. Brain networks associated with higher cognitive functions (such as social and emotional processing) show most pronounced developmental effects, than for example visual, auditory, and sensori-motor systems, which largely mirror adult brain networks (Uddin et al., 2010).

Therefore, one way to look at neurocognitive networks is to investigate spontaneous fluctuations of the BOLD signal when the human brain is at rest. Originally, this *resting-state* literature was *model*-driven and has focused on a-priori hypotheses concerning functional connectivity of a small number of regions of interest (ROIs) and the rest of the brain (*seed-based analyses*). However, the focus has more recently shifted to *data*-driven analyses such as ICA, which emphasise connectivity patterns between multiple ROI within spatially dispersed networks (Cole et al., 2010). These so-called *large-scale* or *resting-state* networks have been reliably detected in healthy individuals, and are based on the assumption that these low-frequency fluctuations (0.01-0.1 Hz) of the BOLD signal represent the state of the

brain when goal-directed behaviour or external input is absent (Damoiseaux et al., 2006b). There has been a debate to whether these networks reflect neuronal connectivity or non-neuronal artifacts (e.g. respiration or heart rate, head motion), concluding that resting-state functional connectivity is thought to broadly mirror structural brain connectivity (Greicius, Supekar, Menon, & Dougherty, 2009) and are minimally contaminated by physiological noise, if data is adequately pre-processed (Van Dijk et al., 2010). Further, ICA analyses allow to separate resting-state fluctuations of the brain from these noise-related BOLD signal variations (Damoiseaux et al., 2006b). Components identified in past ICA studies demonstrate a considerable overlap with task-induced brain connectivity patterns (Smith et al., 2009), and correspond to cortical networks that are involved with visual and auditory processing, motor and executive functioning, memory, as well as the DMN, and the language, dorsal attention, and fronto-parietal system (Damoiseaux et al., 2006b; Van Dijk et al., 2010).

Resting-state functional connectivity is an important indicator for understanding abnormal brain function in mental disorders, and has the advantage of not requiring complicated experimental designs in clinical settings (Damoiseaux et al., 2006a). A common clinical application is to utilise correlation strength between functionally connected brain areas as a marker to how brain systems are integrated (Van Dijk et al., 2010). Decreased signal intensity was found in the insula and dorsolateral ACC during an auditory task, as well as sustained hyper-activation of the DMN during rest in patients with schizophrenia (Nygård et al., 2012). Furthermore, Wotruba et al. (2013) observed functional network alterations in individuals at UHR for psychosis, with at-risk individuals presenting with a loss of task-positive network – task-negative network (TPN-TNN) anti-correlation, and Dandash et al. (2014) reported altered cortico-striatal resting-state connectivity in UHR individuals as compared to HC. Pettersson-Yeo et al. (2011) reviewed the literature on schizophrenia and concluded – despite some inconsistencies - with connectivity reductions across all stages of psychotic disorder.

A systematic review on MD, mainly including ROI-resting-state studies, concluded with altered functional connectivity between areas such as the amygdala, thalamus, and ACC, and on the network level, the DMN, involving the medial prefrontal cortex (mPFC), PCC and parietal cortex (Wang, Hermens, Hickie, & Lagopoulos, 2012). Greicius et al. (2007) confirmed increased functional connectivity within the DMN between the subgenual cingulate, thalamus, orbitofrontal cortex and precuneus. Increased connectivity has further been demonstrated in MD patients in the TPN, specifically in lateral prefrontal and inferior parietal cortices, and in the TNN in the PCC and medial orbitofrontal cortex (Zhou et al., 2009). On the contrary, decreases in functional connectivity have been revealed in medication-free depressed patients using ICA: Thirteen brain networks were identified – 3 of which displayed reduced connectivity in the affective network between the amygdala and anterior insula, and a network associated with attention and working memory of the left frontal pole, and lastly between the lingual gyrus and ventromedial visual areas (Veer et al., 2010). Resting-state analyses of first-degree relatives of individuals with MD showed decreased *regional homogeneity* in the insula and cerebellum as compared to HC (Liu et al., 2010), that is, reduced similarity of time series of voxels in these areas with their nearest neighbours. Aberrant intrinsic functional connectivity has furthermore been observed in individuals with anxiety disorders, such as social anxiety (Liao et al., 2010) and after traumatisation (Lui et al., 2009).

While important for adaptation to acute stressors, prolonged or excessive exposure to glucocorticoids such as cortisol can have damaging neurotoxic effects, such as disruption of synaptic plasticity (Herbert, 1998; Sapolsky, 1999). High levels of cortisol are known to be associated with the development of mental disorders, e.g. to induce severe mood changes (Herbert, 1998). Mondelli et al. (2010) further found that increased cortisol levels at baseline significantly predict smaller left hippocampal volume in first episode of psychosis patients after a 3-months follow-up scan and concluded that biological changes activated by stress, constitute an important factor that influences brain structure. The role of cortisol on brain connectivity in mental disorders has, however, been less illuminated and only studies on

healthy individuals have been reported so far. Thomason, Hamilton, and Gotlib (2011) reported greater cortisol responsivity in healthy adolescents to be associated with higher functional connectivity in the SN after acutely inducing social stress. Increased amygdala - mPFC connectivity was observed in stress responders in another study using healthy volunteers, as well as altered amygdala connectivity with the dlPFC, ACC, anterior hippocampal complex, cuneus, and pre-supplementary motor area (Quaedflieg et al., 2015).

The aim of this study was to extract functional connectivity networks during a resting-state with special focus on the DMN, ECN, and SN due to their relative importance in the development of mental disorders, such as depression and psychosis (Menon, 2011). Furthermore, these networks were tested to whether they show aberrant connectivity in young individuals with mental health problems as compared to HC. Since clinical participants from this sample were on average moderately depressed, and ruminations being a frequent symptom that depressive patients are experiencing, these reoccurring, emotional and self-reflective thoughts were considered to be reflected in increased resting-state connectivity within the DMN in the clinical group (Greicius et al., 2007). Due to the heterogeneity in symptomatology of the clinical sample differences between clinical participants and HC were assumed for the DMN, ECN, and SN, but no directed hypotheses inferred, and these 3 networks instead exploratively looked at. Other networks were aimed to be extracted, but without network alterations between groups being hypothesised. Given the early disease stage and rather mild to moderate clinical symptomatology (as compared to most other studies), clinical participants were further divided into high vs low symptomatology in depressive, anxiety, and psychotic symptoms, psychological distress, and social and role functioning. This was to evaluate whether severity of symptomatology and functional impairment matters in terms of resting-state functional connectivity, with clinical participants in the high symptom and low functioning groups being hypothesised to have more pronounced network alterations as compared to HC (or to be the first to demonstrate alterations as compared to HC). A similar approach was adopted for high versus low cortisol levels in the clinical group since cortisol levels were found to be associated with resting-state

brain function in healthy individuals (Quaedflieg et al., 2015; Thomason et al., 2011), and clinical individuals in the high cortisol group being assumed to have more pronounced network alterations than the low cortisol group as compared to HC (or to be the first to demonstrate alterations as compared to HC).

6.2 Methods

6.2.1 Participants

35 clinical participants who were experiencing psychological distress and 35 HC participated in this study. 1 clinical participant was excluded due to image distortion, and 2 clinical participants and 3 HC due to head motion being greater than 4mm. Both groups were recruited as described in Section 5.2.1 with identical inclusion and exclusion criteria. Interview and self-report measures from the baseline clinical assessment were used, with median time from the first clinical assessment to scanning being 63.5 days (range 5 - 138 days). The study was approved by the local ethics committee and participants gave their informed consent.

Similarly to Section 5.2.2, UHR status, the presence of PLE and threshold psychosis, as well as QIDS, OASIS, K-10, and social and role functioning total scores were further utilised to compare resting-state brain activation of clinical participants by dividing participants into high and low symptom and functioning scores, and comparing both groups with each other, and with HC. Cut-offs and classifications are illustrated in Table 6.1. Clinical participants were further split into high (n = 11) versus low (n = 12) cortisol levels (median = 13.125 pg/mg), and compared with HC to investigate differences in resting-state brain activation.

Table 6.1
Cut-offs for clinical measures and functioning for brain activation comparisons

	High scores	Low scores
CAARMS	Psychotic (n=3) UHR (n=6) PLE (n=8)	No significant psychotic symptoms (n=15)
QIDS	Moderate to severe depressive symptoms (Score ≥11) (n=17)	None to mild depressive symptoms (Score <11) (n=15)
OASIS	Anxiety diagnosis (Score ≥8) (n=24)	No anxiety diagnosis (Score <8) (n=8)
K-10	Severe mental disorder (Score ≥30) (n=19)	Up to moderate mental disorder (Score <30) (n=12)
Social Functioning	Moderate impairment to superior functioning (Score 6-10) (n=21)	Serious impairment to extreme dysfunction (Score 1-5) (n=11)
Role Functioning	Moderate impairment to superior functioning (Score 6-10) (n=17)	Serious impairment to extreme dysfunction (Score 1-5) (n=15)

Notes. CAARMS=Comprehensive Assessment of At-Risk Mental States, QIDS=Quick Inventory of Depressive Symptoms, OASIS=Overall Anxiety Severity and Impairment Scale, K10=Kessler Psychological Distress Scale, UHR=ultra-high risk, PLE=psychotic-like symptoms.

6.2.2   Resting-state analyses

Resting-state scans lasted for 10 minutes, and participants were instructed to lie still. Individuals were asked to close their eyes, whilst letting their mind wander freely without thinking about anything specifically.

6.2.2.1 ICA

Rs-fMRI was chosen as additional indicator for brain function, as it is easy to perform (Song et al., 2011) especially for clients with mental health problems and it provided modest to high intra- and inter-session and multi-scan reliability (Shehzad et al., 2009). Different ways of conducting rs-fMRI analyses have been proposed (Song et al., 2011); in the following Multivariate Exploratory Linear Optimised Decomposition into Independent Components (MELODIC) (www.fmrib.ox.ac.uk/fsl) (Beckmann & Smith, 2004) will be used and described due to its exploratory value for resting-state analyses in a cohort of young help-seeking people with mental health problems, that has not been investigated similarly before.

ICA separates the BOLD signal into spatially independent patterns of brain activity. ICA is based on the assumption that the underlying components are spatially independent and add up linearly. Multivariate techniques such as ICA decompose the fMRI data into spatial maps, which enables the analysis of co-activation in spatially disparate brain regions (McKeown et al., 1998). It is investigated if two or more brain areas have a similar phase of low-frequency fluctuations (0.01 - 0.1 Hz) (Lowe, Mock, & Sorenson, 1998). This decomposition further allows for separation of resting-state networks from physiological noise such as respiration and cardiac cycle (Damoiseaux et al., 2006b).

6.2.2.2 Data acquisition, pre-processing and extraction of brain networks

T2-weighted images were acquired using a 3T Philips Achieva MR scanner (270 dynamics, ascending order, TE = 35 msec, whole-brain coverage, TR= 2.2 seconds, voxel size 2.5 x 2.5 x 3 mm) and high-resolution 3D T1-weighted MRI data was acquired using a 32-channel head coil. T1-weighted images (TR = 8.4 msec, TE = 3.8 msec, flip angle = 8°, FOV = 288 x 232 x 175 mm, voxel size 1 x 1 x 1 mm) were co-registered to the fMRI data for localisation.

Functional scans were analysed using MELODIC software, version 3.14. Default pre-processing steps were applied to the data sets, including brain extraction, highpass-filtering (100s), slice time correction, motion correction (MCFLIRT), normalisation, coregistration with T1 image, and spatial smoothing (FHWH = 5mm). After that, data sets from both groups were concatenated in time to build a single 4D dataset. The data was then decomposed into 19 independent components (IC), describing signal variation across time courses and the spatial maps. A z-score for every voxel and component was computed, which reflects the degree of association between the time series of that voxel and the time series of each component. Permutation of the ICA was conducted 500 times with random conditions. To enable comparison of spatial maps and time courses between the two groups, *GICA 3 back reconstruction* (Erhardt et al., 2011) was employed, a method that evaluates estimation

accuracy to back-construct subject-specific spatial maps and time courses of the decomposition (Michael, Anderson, Miller, Adali, & Calhoun, 2014). The number of IC was chosen after visual inspection and considered to represent the networks of interest in the most informative way. Components were matched with networks of interest, resulting in 11 networks: DMN, SN, dlPFC as part of the ECN, the primary, medial and lateral visual, auditory, sensori-motor, ventral stream, and left and right fronto-parietal network. Group differences were hypothesised for the DMN, ECN, and SN based on a recent review on aberrant brain networks in psychopathological conditions (Menon, 2011), however, hypotheses for none of the other networks could be inferred, and any observed network alterations have to be interpreted with caution due to a lack of relevant literature.

6.2.2.3 Statistical analyses

Dual regression generates subject-specific versions of the spatial maps and associated time series by using spatial maps from group-average analyses. Firstly, a multiple linear regression of the maps of group-average analyses of spatial maps of each component is conducted for each subject, resulting in 4D space-time datasets. Secondly, these time series are normalised and then regressed as temporal regressors in another multiple regression into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. Component activations across patient and control group were then compared for statistically significant differences ($p < 0.05$, FWE-corrected) using FSL's *randomise* permutation-testing tool with 500 permutations (Beckmann, Mackay, Filippini, & Smith, 2009) and TFCE (see Section 5.2.3.3, Smith & Nichols, 2009). Demographic information was compared for clinical participants and HC, using t- and x^2-tests.

6.3 Results

6.3.1 Demographics & description of clinical sample

Clinical participants and HC did not differ in terms of age, gender, handedness, ethnicity, occupation and highest qualification (see Table 6.2).

Table 6.2
Demographic information on clinical participants and HC

	CP (n=32)	HC (n=32)	Test statistic	p-value
Mean age ± SD *(in years)*	20.7±2.5	20.6±2.8	$t(62)=0.191$	0.849
Range	16-25	16-25		
Gender (m/f)	10/22	5/27	$X^2(1)=0.14$	0.237
Handedness (right/left)	27/5	29/2	$X^2(1)=1.342$	0.426
Ethnicity				
White[1]	26	18		
Asian[2]	1	6	$X^2(3)=5.835$	0.12
Black[3]	2	4		
Mixed-race[4]	3	4		
Occupation				
University student[5]	10	16		
College/A-Levels	9	5	$X^2(4)=6.413$	0.17
Unemployed	5	2		
Employed[6]	6	9		
Homemaker	2	0		
Highest qualification				
University[7]	4	9		
A-Levels[8]	16	18	$X^2(3)=5.291$	0.152
GSCE[9]	11	5		
No qualification	1	0		
Psychiatric medication				
Antidepressants	18	0	$X^2(1)=24.421$	<0.001***
Neuroleptics	1	0	$X^2(1)=0.984$	0.321
Beta-blockers	2	0	$X^2(1)=2.001$	0.157
Anticonvulsants	1	0	$X^2(1)=0.984$	0.312

Notes. CP=clinical participants, HC=healthy controls, SD=standard deviation, m=male, f=female
[1] White-British & White-Other, [2] Asian-Pakistani, Asian-Bangladeshi & Other Asian, [3] Black-African, [4] Mixed-Race White-Black-Caribbean, [5] Undergraduate and postgraduate university students, [6] Working full or part-time, [7] Bachelor or Master degree, [8] A-Levels, National Vocational Qualification (NVQ) Level 4, or equivalent, [9] General Certificate of Secondary Education (GCSE, year-10 equivalent) or NVQ level 1 or 2, *** $p < 0.001$.

Clinical participants were on average moderately depressed (QIDS), had an anxiety diagnosis (OASIS) and were in general classified as having a severe mental disorder (K-10). 3 individuals were classified as psychotic, 6 as UHR for psychosis, 8 as having PLE and 15

as having no significant psychotic symptoms according to the CAARMS. Social functioning

was on average moderately and role functioning on average seriously impaired (see Table

6.3).

Table 6.3
Clinical measures (n=32)

Measure	Range	M±SD
CAARMS	0-33	14.8±8.9
QIDS	3-19	10.9±4.3
Ruminative Style	22-40	30.9±5.1
OASIS	1-19	10.0±4.2
K-10 (*n*=31)	18-49	31.6±7.2
Social Functioning	3-9	6.1±1.7
Role functioning	1-9	5.1±2.6

Notes. CAARMS=Comprehensive Assessment of At-Risk
Mental States, QIDS=Quick Inventory of Depressive
Symptoms, OASIS=Overall Anxiety Severity and Impairment
Scale, K-10=Kessler Psychological Distress Scale

6.3.2 Extraction of resting-state networks from single group ICA

A single group ICA which included 32 clinical participants and 32 HC and used 19 IC,

extracted 11 relevant network components comprising of 11 functionally connected networks

of brain areas associated with the DMN (IC 1 & 2), the SN (IC-3), the dlPFC as part of the

ECN (IC-4), right (IC-5) and left (IC-6) fronto-parietal network, the medial (IC-7), primary (IC-

8) and lateral (IC-9) visual, auditory (IC-10), somatosensory (IC-10) and ventral stream

network (IC-11). The extraction of the DMN comprised of a posterior (IC-1) and a frontal

component (IC-2), and the auditory and somatosensory network both constitute one

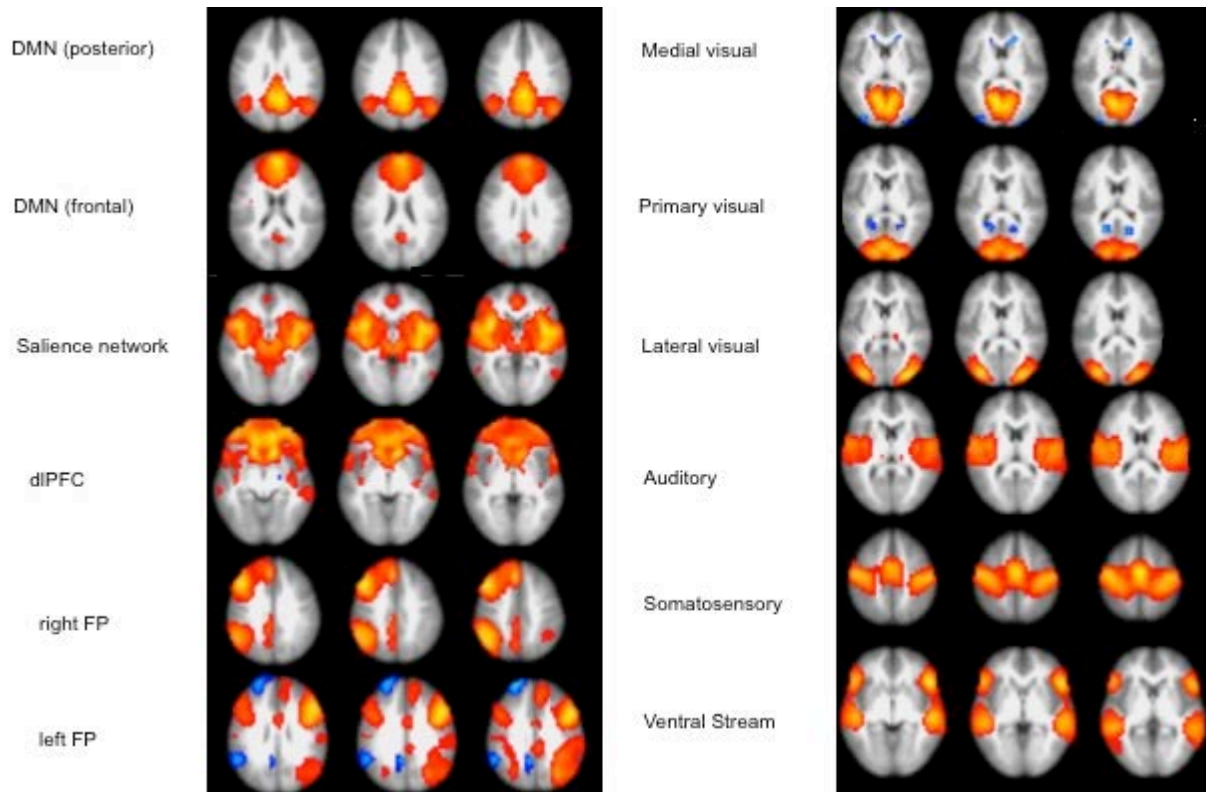component. Networks are illustrated in Figure 6.1.

Figure 6.1. Single group independent component analysis extracting functionally relevant networks in 32 clinical participants and 32 HC. IC-1 (posterior component of default-mode network, *DMN*), IC-2 (frontal component of DMN), IC-3 (salience network), IC-4 (dlPFC as part of the executive control network), IC-5 (right fronto-parietal network, *FP*), IC-6 (left *FP*), IC-7 (medial visual network), IC-8 (primary visual network), IC-9 (lateral visual network), IC-10 (auditory network), IC-10 (somatosensory network), and IC-11 (ventral stream).

6.3.3 Group comparison between clinical participants and HC of extracted brain networks

IC-10 representing the auditory and somatosensory network showed significantly reduced connectivity in the right SMG (MNI coordinates: 34 -42 32, p = 0.036, FWE-corrected) and a trend for reduced connectivity in the left posterior cingulate (-26 -66 12, p = 0.072, FWE-corrected) in clinical participants as compared to HC (see Figure 6.2). No other network demonstrated altered functional resting-state connectivity in clinical participants (all p > 0.05, FWE-corrected).
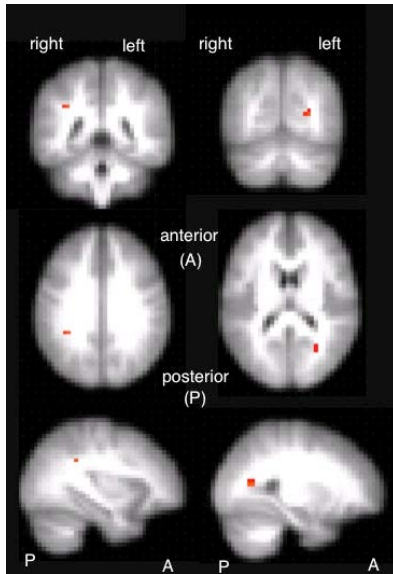
Figure 6.2. Reduced connectivity in clinical participants in IC-10 (auditory and somatosensory network).

6.3.4 Three-group comparison of extracted brain networks

Significant differences in functional resting-state networks are described in the following when splitting clinical participants into high vs low symptom and functioning scores and cortisol levels as described in Section 6.2.1 and comparing the two respective groups with HC.

6.3.4.1 Classification according to psychotic symptoms

Reduced connectivity was found in individuals with high psychotic symptoms as compared to HC in IC-10 representing the auditory and somato-sensory network in the subcallosal cortex (-2 18 -4, p = 0.028, FWE-corrected), STG (10 46 28, p = 0.046, FWE-corrected), PCC (10 -42 0, p = 0.008), SMG (34 -42 32, p = 0.006, FWE-corrected), ACC (-2 18 32, p = 0.038, FWE-corrected), lingual gyrus (-18 -54 0, p = 0.01, FWE-corrected), angular gyrus (38 -54 48, p = 0.03, FWE-corrected), and frontal pole (-26 46 -4, p = 0.04, FWE-corrected), and in IC-11 representing the ventral stream network in the medial frontal cortex (-2 46 -12, p = 0.034 & 2 46 -12 p = 0.034, FWE-corrected), orbitofrontal cortex (14 10-12, p = 0.024 & -18 10 -12, p = 0.03, FWE-corrected), caudate nucleus (6 14 4, p = 0.034, FWE-corrected), insular cortex (38 10 8, p = 0.034, FWE-corrected), SMG (38 -38 4,

p = 0.046, FWE-corrected), middle temporal gyrus (38 -58 12, p = 0.043, FWE-corrected),

occipital fusiform gyrus (38 -62 -8, p = 0.046, FWE-corrected), and occipital pole (30 -90 -8,

p = 0.034, FWE-corrected).

Reduced connectivity was further found in individuals with high psychotic symptoms

as compared to HC in IC-2 representing the frontal part of the DMN network in the inferior

temporal gyrus (IFG) (-38 -58 0, p = 0.04, FWE-corrected). Clinical participants with high

psychotic symptoms showed increased connectivity in the IFG as compared to clinical

participants with low psychotic symptoms (-42 -54 -20, p = 0.046, FWE-corrected).

6.3.4.2 Classification according to depressive symptoms

Similarly to the classification into psychotic symptoms network alterations in the

auditory/somato-sensory and ventral stream network were discovered when splitting clinical

participants into high vs low depressive symptoms: Clinical participants with high depressive

symptoms displayed reduced connectivity in IC-10 in the ACC (10 30 -4, p = 0.048 & -2 18

32, p = 0.02, FWE-corrected) and IC-11 in the angular gyrus (54 -66 32, p = 0.028 & 38 -62

12, p = 0.034, FWE-corrected), temporal lobe (38 -34 4, p = 0.034, FWE-corrected), middle

frontal gyrus (-26 46 -12, p = 0.038, FWE-corrected), and putamen (-26 2 4, p = 0.03 & -26

46 -12 0.038, FWE-corrected) as compared to HC. Reduced connectivity was furthermore

found in IC-5 representing the right fronto-parietal network in the insula (47 6 0, p = 0.046,

FWE-corrected) in clinical participants with high depressive symptoms as compared to

clinical participants with low depressive symptoms.

6.3.4.3 Classification according to anxiety symptoms, psychological distress and cortisol
levels

Reduced connectivity was found in IC-10 representing the auditory/somato-sensory

network in the ACC (2 18 32, p = 0.016, FWE-corrected), SMG (38 -42 32, p = 0.42, FWE-

corrected), and precuneus (-22 -62 8, p = 0.046, FWE-corrected) in clinical participants with

high psychological distress as compared HC. No network demonstrated altered functional

resting-state connectivity in clinical participants with high vs low anxiety symptoms, and high vs low hair cortisol concentrations in the first segment, as compared to HC (all p > 0.05, FWE-corrected).

6.3.4.4 Classification according to social and role functioning scores

Decreased connectivity was found in IC-10 representing the auditory/somato-sensori network in the SMG (34 -42 32, p = 0.048, FWE-corrected) in clinical participants with high social functioning as compared HC. Reduced connectivity was discovered in IC-7 representing the medial visual network in the ACC (-2 2 8, p = 0.048, FWE-corrected) in clinical participants with low social functioning as compared HC. Reduced connectivity was further demonstrated in IC-1 representing the posterior part of the DMN in the IFG (46 38 8, p = 0.048, FWE-corrected), in IC-3 representing the SN in the ACC (-14 38 -4, p = 0.048, FWE-corrected) and in IC-7 representing the medial visual network in the thalamus (-2 2 -4, p = 0.038, FWE-corrected) in clinical participants with low role functioning as compared to HC.

6.4 Discussion

The present study aimed to investigate and compare whole brain functional connectivity in young, help-seeking individuals with early mental health problems, and age, gender, ethnicity, education and highest qualification matched HC during rest. The ICA isolated the DMN, SN, part of the ECN with the dlPFC, the primary, medial and lateral visual, auditory, sensori-motor, ventral stream, and left and right fronto-parietal network during rest. Contrary to the hypothesis, the clinical group did not display increased functional connectivity of the DMN during rest as compared to HC. However, the IC representing the auditory and somatosensory network displayed significantly reduced resting-state connectivity in the SMG and a trend for reduced connectivity in the posterior cingulate. Clinical participants with (sub-)threshold psychotic symptoms showed significantly reduced connectivity in the frontal part of the DMN, ventral stream and auditory and somatosensory network as compared to HC, and clinical participants with moderate to severe depressive symptoms showed similarly decreased connectivity in the auditory and somatosensory and ventral stream network as compared to HC, as well as in the right fronto-parietal network as compared to clinical participants with none to mild depressive symptoms.

This study supports the idea that the resting state of the brain is not an inactive, but rather a dynamic state with coherent slow fluctuations of the BOLD signal (Damoiseaux et al., 2006a), by demonstrating the existence of 11 networks in both young patients with mental health issues and HC. The isolation of diverse resting-state networks, such as the DMN, SN, visual, auditory, sensori-motor, ventral stream and fronto-parietal networks, is mainly consistent with other previous ICA, e.g. in accordance with Veer et al. (2010) who identified 13 relevant networks using a 20 component ICA in depressed patients and HC. In this study, 11 relevant networks were identified using a 19 component ICA. In contrast to Veer et al. (2010), the current study identified the DMN with two components, instead of a single one. Achieving one component proved to be difficult with this data set, and therefore resulting in posterior and anterior nodes for the DMN. DMN regions are responsible for various operations (e.g. autobiographical, self-monitoring, social functions (Menon, 2011))

and so, although coherent on average, components have a degree of independent activity as well.

The current study highlights the relevance of the auditory and somatosensory network in young people who are help-seeking for mental health problems, such as the SMG and potentially the posterior cingulate, however, resting-state connectivity of no other network was altered when comparing clinical participants with HC. In contrast to other studies, altered functional connectivity was not discovered, as e.g. decreased connectivity within networks relevant for affect regulation, attention and working memory (Veer et al., 2010), or increased connectivity between cingulate, frontal and parietal regions in depressed patients (Greicius et al., 2007; Zhou et al., 2009).

When splitting the current sample into none to mild, and moderate to severe depressive symptoms, and focusing on brain areas instead of networks, decreased functional connectivity was discovered for the moderate to severe group in areas such as temporal and frontal regions and the insula, similar to areas discovered in Veer et al. (2010), yet, as part of different brain networks. The findings are, however, in contrast to increased connectivity as shown by Greicius et al. (2007) and Zhou et al. (2009), and in contrast to the initial hypothesis of increased connectivity in the DMN due to ruminations. Zhou et al. (2009) included medication-free patients, and Greicius et al. (2007) included severely depressed patients. Furthermore, only Veer et al. (2010) included dual regression as method to compare groups, whereas Greicius et al. (2007) used ICA but not dual regression, and Zhou et al., (2009) used seed-based analyses. The current study included on average moderately depressed clinical participants of which more than half were taking antidepressants at the time of scanning. Both, less severe depressive symptoms, and the effect of antidepressant treatment, as well as the comparatively young age and early stage of illness could account for the absence of functional connectivity increases in the DMN and similar areas as seen in Greicius et al. (2007) and Zhou et al. (2009), as well as methodological differences in the analyses.

Similarly, no group differences were discovered as in other studies on schizophrenia (Nygård et al., 2012) and the UHR state of psychosis (Dandash et al., 2014; Wotruba et al., 2013). This might be due to the fact that brain alterations in threshold schizophrenia are more pronounced than in the earlier stages of mixed mental health problems. Furthermore, only approximately half of the clinical sample presented with some sort of significant psychotic symptoms.

Nygård et al. (2012) discovered sustained hyper-activation of the DMN during rest and decreased connectivity in the insula and dorsolateral ACC in patients with schizophrenia as compared to controls, Wotruba et al. (2013) showed that individuals at UHR for psychosis showed a loss of TPN-TNN anti-correlation, and Dandash et al. (2014) altered cortico-striatal connectivity - no such differences were detected in the current study when comparing clinical participants with HC. The current study did not replicate those findings, possibly due to methodological differences: Wotruba et al. (2013) and Dandash et al. (2014) used a model-driven approach by implementing seed-based analyses, whereas the current study and Nygård et al. (2012) analysed data-driven by implementing an ICA. However, some of the areas that have been identified to be altered in those studies, were found in the current study as well, when splitting the clinical sample into (sub-)threshold psychotic symptoms as compared to HC, such as the caudate nucleus as striatal structure, the ACC, and DMN regions such as the PCC and angular gyrus. Most connectivity alterations were discovered to be between clinical participants in the high symptom and low functioning groups, as hypothesised to be the first to demonstrate alterations as compared to HC (in contrast to low symptomatology and high functioning). The finding of mostly decreased connectivity in individuals with (sub-)threshold psychotic symptoms as compared to HC is further consistent with a trend for connectivity reductions across all stages of psychotic disorders as reviewed by Pettersson-Yeo et al. (2011).

Whilst prolonged or excessive cortisol excretion has been associated with the development of mental disorders (Herbert, 1998) and with changes in brain structure in mental disorders such as schizophrenia (Mondelli et al., 2010), no such differences were

discovered in the current study with regards to the role of cortisol for brain connectivity analyses in early mental health disorders. The scarcity of studies in this field led to hypotheses being based on findings from studies of acute stress and cortisol increases in healthy individuals (Quaedflieg et al., 2015; Thomason et al., 2011). It is possible that longer-term increased cortisol levels in the course of early mental health problems do not elicit the same effects on brain connectivity as acutely induced stress in healthy individuals. Furthermore, cortisol was only used as a grouping variable instead of a covariate due to methodological issues, that is a median split was conducted to classify into clinical participants with high and with low cortisol levels as compared to HC.

There are several limitations to this study. Firstly, the conduction of multiple comparisons has to be acknowledged. Similarly to Section 5.4, stringent FWE-correction was used for within-analysis comparisons on the voxel-level, but multiple comparisons were conducted for dividing the clinical group into high vs low scores for clinical and functioning measures, and hair cortisol levels, each consisting of six contrasts, respectively. Even though the main finding of reduced connectivity within the auditory and somatosensory network was replicated in clinical participants, e.g. when dividing clinical participants into high versus low psychotic and depressive symptoms, this network was not one to be a-priori hypothesised to show alterations. Network alterations of subgroup analyses which were not shown when comparing clinical participants and HC, and which were not a-priori hypothesised, such as the medial visual network (when comparing the low social functioning with HC group), may constitute this sort of false-positive artefacts and have to be viewed with special caution. However, it is noteworthy that differences in the auditory and somato-sensori network showed up quite consistently in the high symptomatic groups as compared to HC, indicating a subtle but robust finding for reduced connectivity. Secondly, due to the explorative nature of this study, only one hypothesis was inferred. Studies on resting-state functional connectivity in threshold disorders have been conducted (e.g. schizophrenia) but often using different methodology, e.g. regional homogeneity or ROI approaches, complicating the deduction of clear hypotheses. With ICA being a data-driven approach,

relevant differences would have been detected without explicit hypotheses, minimising the likelihood of missing relevant network alterations. However, the caveat with the approach undertaken lies in balancing the right number of IC when setting the analyses. The aim was to obtain networks of interest, e.g. the DMN, ECN and SN, maximising the number of all potentially relevant networks, and yet splitting network nodes into as few components as possible. This was achieved by using 19 components. Secondly, physiological noise, such as head motion, heart rate and breathing was not monitored whilst scanning. Therefore it is not clear whether group differences in these variables have accounted in any way for no further significant differences in brain networks between clinical participants and HC. However, ICA decomposition allows for separation of resting-state networks from physiological noise (Damoiseaux et al., 2006b) making it unlikely that group differences in network organisation would have been observed if physiological measures were taken. Thirdly, medication intake was not controlled for and clinical participants presented with unspecific mental health symptoms creating heterogeneity in clinical presentation. However, the aim of this study was not to look at diagnostic categories but at how the human brain functions at rest in the early stages of mental health problems. This only complicates comparison with other studies investigating threshold disorders or clear-cut stages when looking at mental health on a continuum, e.g. the UHR state for psychosis (Wotruba et al., 2013).

In conclusion, the ICA demonstrated commonly found resting-state brain networks in young individuals with early mental health problems and HC. The auditory and somatosensory network displayed significantly reduced resting-state connectivity in the SMG and a trend for reduced connectivity in the posterior cingulate. Clinical participants with (sub-)threshold psychotic symptoms and with moderate to severe depressive symptoms showed significantly reduced connectivity in networks such as the auditory and somatosensory network, and ventral stream as compared to HC. Functional resting-state connectivity in the whole clinical group was largely intact, and more pronounced network alterations became only apparent when considering symptom severity. Longitudinal studies

with larger samples are needed to address how certain diagnostic groups of mental

disorders are related with altered functional connectivity in specific networks and when in the

course of illness these alterations become apparent.

CHAPTER SEVEN

GENERAL DISCUSSION

7.1 Overview

Even though having proven useful in medical (e.g. cancer) research, clinical staging has only recently been introduced into psychiatric disciplines. Psychiatric staging models have been proposed, yet only limited and preliminary validation has taken place so far. This thesis aimed to integrate neurobiological parameters into the early stages of a clinical staging approach: Youths with mental health problems shared their perceptions, feelings and thoughts that helped to assess the level of depressive, anxiety and psychotic symptoms and functioning at the first clinical study contact and after 3 and 6 months, which were reported in the first and main study. The following studies were built on the clinical data of the first study, and extended it with neurobiological assessments. The second study investigated hair cortisol concentrations and the third and fourth study looked at brain activation during working memory processes and during rest. Both hormonal levels and brain maturation undergo extensive changes during the period of adolescence until young adulthood, and both have been found to be associated with the onset of mental disorders. These neurobiological parameters shall be integrated into the concept of clinical staging, focusing on the early stages of mental ill health. Clinical variables and functioning will be used as dimensional (e.g. total scores of individual interview and self-report data) and categorical (e.g. classification into UHR for psychosis) information, in order to discern associations amongst these variables and with neurobiological factors in the pathogenesis of early mental health problems.

7.2.1 Summary of neurobiological findings into clinical staging

Findings from Chapter 4 suggested elevated hair cortisol concentrations representing the past three months of exposure in adolescents and young adults with early mental health

problems compared to healthy participants. Perceived stress was also elevated in clinical participants, yet there was no association between cortisol and perceived stress experience, and cortisol was only significantly correlated with psychological distress. This may be explained by perceived stress scales inquiring information about subjective stress experiences, whereas psychological distress rather relates to depressive and anxiety symptoms that may be experienced by the individual, and therefore possibly being a more objective measure, as is cortisol itself.

The n-back task, as described in Chapter 5, activated mainly frontal, but also parietal and marginally subcortical brain regions in HC and clinical participants such as the superior, middle, and orbito-frontal areas, SMG, ACC, and basal ganglia, which overlapped with those areas typically detected as relevant for a verbal working-memory task in previous literature, such as the dlPFC, and PCC (Owen et al., 2005). Clinical participants with mental health issues showed a reduced response in the SFG, ACC, insula, putamen and hippocampus, however, no hyper-activation was detected in clinical participants. Comparing clinical participants with high symptom and low functioning scores to HC replicated the finding of hypo-activation, however, of more distributed brain areas. No behavioural group differences in reaction time and accuracy, and no associations with cortisol levels, were detected.

Chapter 6 aimed to investigate and compare whole brain functional connectivity during rest. The ICA isolated the DMN, SN, part of the ECN with the dlPFC, the primary, medial and lateral visual, auditory, sensori-motor, ventral stream, and left and right fronto-parietal network during rest. The IC representing the auditory and somatosensory network displayed significantly reduced resting-state connectivity in the SMG and a trend for reduced connectivity in the posterior cingulate. Clinical participants with (sub-)threshold psychotic symptoms showed significantly reduced connectivity in the frontal part of the DMN, ventral stream and auditory and somatosensory network as compared to HC, and clinical participants with moderate to severe depressive symptoms showed similarly decreased connectivity in the auditory and somatosensory and ventral stream network as compared to

HC, possibly indicating that symptom severity of depressive and psychotic symptoms influences the magnitude of resting-state connectivity alterations. No association with cortisol levels was detected.

Considering the different nature of the composition of the current sample with youths with early and unspecific mental health problems who have not been assigned a clinical diagnosis for the analyses, these findings are in agreement with some other studies using diagnostic classification systems. Previous studies have mostly included individuals with clear diagnoses such as depression and schizophrenia, or classified individuals as UHR for psychosis. However, the hair cortisol findings of the current studies are consistent with elevations found in clinically depressed individuals (Dettenborn et al., 2012), as opposed to anxiety disorders which have been found to manifest in both hyper- and hypocortisolism (potentially due to time elapsed between onset of anxiety disorder and/or trauma, with higher cortisol levels soon after onset, and a decline below normal as time passes) using hair analyses (Steudte et al., 2011a; Steudte et al., 2011b). Almost all clinical participants of the current study were somehow, and on average moderately depressed, which is in agreement with Dettenborn et al. (2012). The majority of the current sample was assigned to have the severity of anxiety symptoms as seen when an anxiety diagnosis is given, however, comparison with other findings is complicated since no differentiation into anxiety disorders took place and the presence of (recent) traumatic events was not controlled for, whose timing majorly impacts on HPA axis functioning, e.g. in terms of hyper- and hypo-cortisolism.

Despite inconsistent results concerning brain activation during working memory processes with activation increases and decreases in schizophrenia and depressed patients, and their healthy siblings, the current findings of hypo-activation of diverse frontal, parietal and subcortical areas, are e.g. consistent with less activation (e.g. in the thalamus, precentral gyrus and parietal cortex) (Barch et al., 2003) and of the medial frontal gyrus, precuneus, PCC, thalamus and hippocampus in healthy siblings of schizophrenia patients (Callicott et al., 2003a). Even though the current findings of e.g. hypo-activated superior,

middle, and orbito-frontal areas in youths with mental health problems as compared to HC, are consistent with the general idea of hypo-frontality in schizophrenia (Pettersson-Yeo et al., 2011), since about half of the clinical sample displayed (sub-)threshold psychotic symptoms, no differences in brain activation were found when splitting the clinical sample and comparing those with (sub-)threshold psychotic symptoms with clinical participants with no significant psychotic symptoms. However, reduced brain activation during working memory processes was apparent when comparing clinical participants with high psychotic symptoms with HC in the SFG, hippocampus and caudate nucleus, and clinical participants with low psychotic symptoms with HC in the post-central and middle temporal gyrus and ACC. Differences in brain connectivity during rest were likewise apparent, e.g. in the auditory and somatosensory and ventral stream network between clinical participants with high psychotic symptoms and HC. The general finding of subtle hypo-connectivity of the SMG and potentially posterior cingulate, further supports the functional dysconnectivity hypothesis in schizophrenia (Stephan et al., 2006) which, however, clearly involves more pronounced alterations in threshold disorder as compared to the current sample of assumably sub-threshold distress disorders.

Hair cortisol levels of the first segment representing the past 3 months prior to MRI scan were hypothesised to moderate brain activation during working memory and undirected mental activity, since acute psychosocial stress was found to impair working memory performance in healthy participants (Luethi et al., 2009) and elicited reduced activity in the dlPFC and reduced deactivation of the PCC and orbitofrontal cortex (areas constituting the DMN) during working memory processes (Qin et al., 2009). Thomason et al. (2011) reported greater cortisol responsivity in healthy adolescents to be associated with higher functional connectivity in the SN after acutely inducing social stress, and altered connectivity between the amygdala and PFC and other cortical regions was observed (Quaedflieg et al., 2015). Therefore, chronic stress, as measured by means of hair samples, was hypothesised to correlate with activation of brain areas involved in working memory (such as the dlPFC) and clinical individuals with high cortisol levels being assumed to have more pronounced network

alterations than the low cortisol group as compared to HC. Neither hypothesis held true, possibly due to the fact that hypotheses were based on studies including healthy participants as compared to clinical samples and psychological stress was acutely induced instead of naturally occurring during an extended period of time, as measured with the hair analyses.

7.2.2 Relevance of functioning for UHR and clinical staging

As demonstrated in Chapter 3, psychotic-(like) symptoms in help-seeking young people appear to be associated with more severe depressive symptoms and poorer functioning. However, *UHR status* for psychosis did not differentiate severity of depressive and anxiety symptoms and functioning: No differences were found between UHR clinical participants and those with only PLE and no significant psychotic symptoms for the severity of depressive or anxiety symptoms, and functioning. This indicates it is the overall *severity* and *frequency* of psychotic(-like) symptoms exerting the effect on depressive and anxiety symptoms and functioning, and not the classification as UHR for psychosis per se that matters, which gives indirect evidence against including the functioning criterion for UHR classification and clinical staging in general. However, this conclusion should be considered with great caution due to the for this research question comparatively small sample sizes and the preliminary nature of the of the study design.

7.2.3 Summary of relevance of approaches to youth mental health

Issues that are associated with categorical approaches (Section 1.3.1) to mental health have proven to exist in the current sample, such as co-occurrence of symptoms: About two fifths presented with both depressive and psychotic(-like) symptoms and about three fifths experienced depressive symptoms whilst classified as having an anxiety diagnosis and one forth was diagnosed with an anxiety disorder whilst experiencing psychotic(-like) symptoms at baseline. Despite the fact that the current sample did not

present with threshold disorders, such as schizophrenia, it can be said that these symptom sets co-occur instead of isolatedly occurring in individuals.

The description of the current sample is in accordance with McGorry (2013) who summarises that mental disorders are considered to be dynamic syndromes that overlap and share aetiologies and courses. Major psychiatric disorders are in this regard often said to be preceded by prodromes, consisting of non-specific symptoms, such as anxiety and depression, frequently being associated with persistent stress and disability. Depending on whether clinical participants of this sample go on to develop threshold disorder, the term *prodrome* will hold true, whereas for the remainder the term *sub-threshold distress disorder* may be more accurate.

Even though the current studies did not provide any evidence to evaluate the *bifactor model* (Brodbeck et al., 2011, see Section 1.3.3) and the idea of ideographic and nomothetic parameters (that is, individual-specific profiles and group-based classifications, Wigman et al., 2012, see Section 1.3.4) of mental health, the idea of a general distress factor underlying depression and anxiety (and psychotic) symptoms relates to the overlap of depressive and anxiety (and psychotic) symptoms of the current sample (Sections 3.3.5 and 3.3.6).

To conclude, both dimensional and categorical approaches are needed to observe the overlap in biosignatures and risk factors across psychiatric disorders (Keshavan et al., 2014). Despite sharp criticism of categorical approaches in the recent past, neither the merit of categorical approaches is disputable, nor is clinical staging inherently different, e.g. from the DSM, especially with including the consideration of symptom severity in the DSM-V (American Psychiatric Association, 2013). Dimensional approaches, such as clinical staging (e.g. McGorry et al., 2007) or the notion of a general construct underlying psychopathology (Brodbeck et al., 2011; Wigman et al., 2012) add to the knowledge about the development of mental disorders and are meant to refine diagnosis and treatment selection, and not entirely replace existing systems.

8.3 Methodological considerations

This thesis used data from a cohort of young individuals with early mental health problems, who were followed up after 3 and 6 months. Those individuals who had a family history with a first-degree relative with mental health problems and/or whose problems did not improve within 6 weeks after the baseline assessment according to self-report, were included in the neurobiological assessments. These youths underwent fMRI scans and/or donated hair samples within 7 months after the clinical baseline assessment and were compared to a group of mentally healthy youths without a family history of mental problems. Strengths and weaknesses of this thesis and studies that were included, are discussed in the following.

8.3.1 Strengths

This thesis combined different methodological modalities that complemented each other: Self-report and interview data from the first study were included as correlates and covariates in the neurobiological chapters. Depressive, psychotic, and anxiety symptoms, psychological distress, and functioning were correlated with cortisol concentrations to discern whether increased cortisol levels in clinical participants were driven by or otherwise related to these individual factors rather than the underlying component of unspecific symptoms during the early stages of mental health problems. Furthermore, the objective nature of cortisol levels and fMRI data added to the rather subjective, and bias-prone self-report information. A relatively large sample size is another strength of this thesis (clinical assessments: $n_{Baseline} = 73$, $n_{6\ months} = 55$) when considering the longitudinal nature and detailed information that has been gathered in the course of clinical assessments, as well as for a neuroimaging study (n = 70).

Large cohort studies on youth mental health and clinical staging have been published in the past years, however, to date this thesis is amongst the first attempts to integrate neurobiological markers into the early stages of the clinical staging model of mental disorders (e.g. McGorry et al., 2007). Furthermore, findings from this thesis existing literature supplement on rather chronic mental health conditions in comparatively older individuals,

often with repeated episodes of mental health disorders (e.g. Barch et al., 2003; Staufenbiel et al., 2013; Wang et al., 2012), genetic risk studies (e.g. Callicott et al., 2003a; Liu et al., 2010; Mannie et al., 2010), and UHR for psychosis (e.g. Goghari et al., 2014; Wotruba et al., 2013).

8.3.2 Weaknesses

A major issue of the neurobiological part of this thesis is the absence of clinical information for the control group. Even though HC were screened for present and past mental disorders, sub-threshold distress - which does not yet meet diagnostic criteria – may have existed. This lack of clinical data for controls restricted correlational analyses and ANCOVA to the clinical group only, resulting in low power of the analyses and relocating the analyses to the more pronounced end of the continuum of mental health symptoms. However, the clinical group experienced self-reported distress at a level significant enough to reach secondary care, indicating that clear-cut differences between the two groups existed. Despite some potential symptomatology in the control group, are the groups in fact very different.

The time window of follow up assessments was comparatively short with 6 months for the clinical chapter, and only a cross-sectional design was used for the neurobiological chapters. Slow recruitment rates for these studies were, among other factors, down to limited access to health services amongst individuals with mental health problems (McGorry et al., 2014), which in turn, impeded opting for a more extensive follow-up period and a prospective design for the neurobiological chapters. Youth mental health, however, is a fairly new discipline and evidence for better health outcomes and economical benefits with this new mental health approach are required, but difficult to achieve given the long-term nature of validating mental health outcomes. Longitudinal studies are therefore needed to replicate current findings within a larger scope and time frame. The implementation of such studies is

encouraged by pioneering work of evidence-based staging and early intervention in psychosis (McGorry et al., 2014).

The neurobiological assessments took place up to 7 months after the first clinical assessment. Therefore, clinical and functioning variables that were used for the analyses, were extracted from the clinical baseline assessment. This option was chosen - despite producing a comparatively large gap - as compared to using the closest clinical assessment (e.g. 3 or 6 months follow-up) - because the interest lay in clinical stage classification which usually happens at the first clinical contact, and further, because little is known about dynamic staging over time. Considering the improvement of the current sample regarding clinical symptomatology, if individuals were staged later in the course of the study, it is likely that earlier stages would have been assigned.

The measures which were selected in accordance with similar cohort studies conducted in Australia, to yield consistency and comparability, constitute a further limitation. First of all, the measures capture symptoms for varying time periods from 2 days to 12 months, which complicates to compare the impact of different symptom sets with each other. Secondly and related to this, issues exist with individual measures such as the QIDS: Even though depressive symptoms may have been present for which the individual sought help, these symptoms have not necessarily been covered, since the QIDS refers to the past week only. This fact is especially of interest because of a likely gap of days up to weeks between recruitment and actual clinical assessment.

Measures that related to mania, eating and substance use symptoms were excluded from this thesis (despite being included as branches in the *Trunk and Branches model*), for example, due to methodological reasons, e.g. the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978) covered manic symptoms for the past 2 days only, and the SCOFF (acronym for the items, Luck et al., 2002) was supposed to cover eating disorders with a rather minimalistic number of 5 items. Substance use disorders were excluded due to small numbers of stage classifications according to the ASSIST (Humeniuk et al., 2008) in the current sample. This constitutes another simplification of the underlying heuristic

representation of the clinical staging model (despite being a necessary exclusion), and takes potential explanatory value from the respective analyses.

Finally, as a minor limitation to mention is that 4 clinical participants who were originally classified as experiencing a FEP (in the main study and for consequent sub-analyses in the neurobiological chapters), were submerged with UHR for psychosis and PLE for practical and statistical reasons, depending on the existence of functional impairment. Therefore there are two options possible: these individuals were either actually experiencing a psychotic episode and therefore correctly detected as FEP, but incorrectly included in the current analyses, or correctly included in the analyses but constituting type 1 classification errors when using the CAARMS. Nevertheless, this concerned a comparatively small number of participants only, and was a necessary adjustment for the respective analyses.

8.4 Implications for future research

Research on individuals at UHR for psychosis has shown that there is a need to start looking at cohorts of young people without focusing on diagnostic categories in the first instance. Psychological distress and the need for clinical care often exist long before a threshold diagnosis has been assigned – not only for those at risk for developing psychotic disorders. Therefore, studies have started to emerge on practicing clinical staging in young people for a variety of mental disorders, however, these are only yet in the fledging stage and need further refinement and replication.

This thesis can be seen as a first step with the superior goal of establishing neurobiological markers and looking at boundaries of clinical measures in order to refine and validate the clinical staging model for mental disorders. A second step would explicitly test cut-offs of clinical measures, e.g. by using latent class analyses in recognising meaningful and definable sub-populations (Jung & Wickrama, 2008) in the larger and heterogeneous group of individuals with mental disorders. In simple terms, this means creating algorithms to use clinical variables in order to assign clinical stages to individuals. These sub-populations

are thought to focus on progression of illness, and only in a second instance, when illness has progressed beyond a significant threshold (*stage 2*), on classifying into rather common categories of mental disorders (psychosis, depression, mania, anxiety, substance use, and eating disorders). Whereas this thesis included individuals considered to be in the early stages (e.g. *stage 1a* and *1b*) and focused on neurobiological correlates in these early stages, more work needs to be done on whether preliminary cut-offs are valid boundaries between stages, e.g. which clinical measure scores are valid cut-offs to differentiate between sub-threshold distress (*stage 1b*) and threshold disorder (*stage 2*) and whether receipt of evidence-based treatment (e.g. cognitive-behavioural therapy or psychiatric medication) is a necessary condition for assignment to *stage 2*. This modelling of developmental trajectories with latent class analyses requires extensive datasets with longitudinal variables, aiming to investigate variation between individuals in intra-individual transition over time (Jung & Wickrama, 2008).

Continuous longitudinal follow-up is needed to not only follow transition to stage 2, but also to validate landmarks for remission and incomplete remission (stage 3a), relapses after remission (*stage 3b & 3c*), non-response for treatment and persistent disorder (*stage 4*). Other neurobiological markers such as sex hormones (e.g. testosterone, progesterone, estradiol), structural grey and white matter connectivity, and performance and brain activation during other cognitive functions (e.g. social cognition, attention, decision making) are further related to the development and phenotype of mental disorders.

Lastly, one important factor that has been neglected in this thesis, and which should be considered for future research in similar psychiatric populations, is *sleep*: abnormal sleep duration has repeatedly been shown to severely affect individuals' health, cognition and mood (Waters & Bucks, 2011). Sleep disturbance frequently accompanies psychiatric disorders and likely affects their course (Krystal, Thakur, & Roth, 2008). Further, sleep deprivation in healthy individuals has been reported to increase evening cortisol levels (McEwen, 2006), and negatively affect cognitive processes as demonstrated in fMRI studies (Chee & Chua, 2008).

8.5 Implications for clinical practice

This thesis, which is embedded in a larger clinical staging model for mental disorders, has also implications for "diagnosis" and treatment in clinical practice. However, the term *diagnosis* appears in this context not entirely appropriate, especially when looking at young people in the early stages, presenting with psychological distress and unspecific psychiatric symptoms and/ or UHR features. In these cases, focusing on symptoms (rather than *syndromes* or *diagnoses*), impairment and actual help-seeking behaviour might be indicated, to conclude about treatment options. Whereas need for care has usually been based on threshold diagnosis, this clinical staging model suggests that need for care exists before threshold disorder. This idea is supported by the fact that most clinical participants from the current cohort were considered to be stages 1a and 1b, due to their young age and seeking professional help for their mental health problems. Furthermore, individuals were not recruited from UHR clinics, but a considerate proportion displayed UHR features or PLE (1/4 were classified as UHR for psychosis and an additional 1/5 as experiencing PLE in the main study). This suggests that even though psychotic(-like) experiences were generally not the reason why clinical participants sought help, they need additional consideration from mental health professionals, as they have the potential to cause significant distress and impairment. The findings of increased perceived stress and cortisol levels and subtle alterations in brain activation during working memory processes and rest add to the notion of need for care on the grounds of emerging neurobiological abnormalities.

According to the clinical staging model neurobiological parameters are considered to have potential for the refinement of treatment selection. This thesis has given an impetus for using cortisol levels and brain activation during working memory and rest, to refine treatment selection. Even though no data is available to compare the early and later stages of mental health problems, it appears that individuals with early mental health problems are distinct on average by increased cortisol levels and subtle alterations of brain activity during working memory and rest from HC (see Chapters 4 to 6). Early intervention, e.g. during the UHR state for psychosis, has amongst others, the purpose to delay or prevent transition to

threshold disorder (Fusar-Poli et al., 2012). It is especially relevant in this regard, to distinguish those individuals who will go on to transition from those who will not, considering the burden and impairment of threshold disorder. Interview measures such as the CAARMS have good (Yung, Phillips, Yuen, & McGorry, 2004) - but not perfect - sensitivity and specificity. Therefore identification based on more objective neurobiological correlates, offers improvement in sensitivity to detect prodromal cases and prevent or delay transition, and specificity to prevent overtreatment for those individuals who may only need treatment based on actual symptom presentation. This thesis offered some preliminary evidence that more severe clinical symptomatology and functional impairment is associated with, e.g. more pronounced changes in brain activation. It has, however, been beyond the scope to longitudinally assess whether those who are more impaired are more likely to have a worse clinical and functional outcome later on. Further research is needed to make use of neurobiological correlates in addition to already established measures, to support guiding treatment and employing a sequential approach. Ultimately, risk-benefit considerations (e.g. in case of uncertainty when using self-report and interview data) could potentially be supported by neurobiological correlates to guide treatment selection.

8.6 Conclusion

Clinical participants from this study were recruited from general early intervention services, however, one fourth were classified at UHR for psychosis and another fifth presented with (sub)threshold psychotic symptoms without functional decline. UHR classification did not appear to be crucial in predicting need for clinical care among these youths seeking help for mental health problems. Intensity and frequency of psychotic symptoms, however, partly predicted clinical symptoms in the short-term. This period of early and rather unspecific mental health problems was associated with significantly increased perceived stress, and increased cortisol levels over the past three months. Despite no behavioural differences, clinical participants showed a subtle hypo-activation of the SFG,

anterior cingulate, insula, putamen and hippocampus and reduced resting-state connectivity in the auditory and somato-sensori network in the SMG. Grouping clinical participants into high vs low symptoms and functioning replicated findings for brain activation for the working memory paradigm with more dispersed hypo-activated brain areas and led to additional resting-state network alterations, especially when comparing the high symptom and low functioning groups with HC.

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APPENDICES

A-1   Poster advertising the Transitions Study

A-2   Leaflet advertising the Transitions Study

A-3   Information for clinicians and staff supporting recruitment of the Transitions Study at the ▉▉▉▉▉▉▉▉▉▉▉▉▉

A-4   Letter to clinical participants – "pre-consent form"

A-5   Participant information sheet for the Transitions Study

A-6   Participant consent form (older than 16 years) for the Transitions Study

A-7   Participant consent form (younger than 16 years) for the Transitions Study

A-8   Parent and guardian consent form for participants younger than 16 years for the Transitions Study

A-9   Poster advertising the neurobiological add-on study of the Transitions Study targeting healthy controls

A-10   Letter of invitation for neurobiological add-on study of the Transitions Study

A-11   Letter of invitation for follow-up of the neurobiological add-on study of the Transitions Study

A-12   Participant Information sheet for clinical participants for the neurobiological study

A-13   Participant consent form (older than 16 years) for clinical participants for the neurobiological study

A-14   Participant consent form (younger than 16 years) for clinical participants for the neurobiological study

A-15   Parent and guardian consent form for clinical participants younger than 16 years for the neurobiological study

A-16   Participant information sheet for healthy controls for the neurobiological study

A-17   Participant consent form (older than 16 years) for healthy controls for the neurobiological study

A-18   Participant consent form (younger than 16 years) for healthy controls for the neurobiological study

A-19   Parent and guardian consent form for healthy controls younger than 16 years for the neurobiological study

APPENDIX B: QUESTIONNAIRES AND MEASURES

B-1   Tracking information

B-2   Health service use information

B-3   Family history of psychological disorder

B-4   QIDS

B-5   ASSIST

B-6   CAARMS

B-7   SOFAS

B-8   Global Functioning: Social Scale

B-9   Global Functioning: Role Scale

B-10   Physical measurements (height, weight)

B-11   Demographics, education, work

B-12   Ruminative style

B-13   CTQ

B-14   K-10

B-15   OASIS

B-16   SCID-I

B-17   Screening for hair steroid analysis and additional MRI session

B-18   MRI safety screening questionnaire

B-19   Scanning documentation

B-20   Perceived stress scale (PSS)

THE UNIVERSITY OF BIRMINGHAM

TRANSITIONS

WOULD YOU LIKE TO TAKE PART IN RESEARCH?

WE ARE LOOKING FOR YOUNG PEOPLE (AGES 14-25) WHO ARE SEEKING HELP FOR MENTAL HEALTH ISSUES OR ARE CONCERNED ABOUT THEIR MENTAL HEALTH TO TAKE PART IN A STUDY RUN BY THE UNIVERSITY OF BIRMINGHAM.

What does the research involve?

·We would like to interview you about your **personal history** and **symptoms**

·We would like to see you a few times

·You will receive **£20 each time**

·Assessments take about **1 to 2 hours**

·All information is **confidential**

WANT TO KNOW MORE?

➤Call or text us:

➤ Email us on

➤ Facebook message us:

CAN EVERYONE TAKE PART IN THIS STUDY?

We may not be able to talk to everyone who wants to take part in the study. If we are not able to talk to you, we will write and let you know.

WHAT IF THERE'S A PROBLEM?

If there is a problem during the study, the research team can be contacted during 9-5pm Mon-Fri. If you need to speak to someone about urgent mental health problems outside of these hours, you should call NHS Direct on 0845 4647.

WHO IS RUNNING THIS STUDY?

This research is being carried out by researchers at the School of Psychology, University of Birmingham.

WANT MORE INFORMATION?

Then please contact The Transitions Study team:

Kareen Heinze
Doctoral Researcher

Text or call:

Email us:

Facebook message:

TRANSITIONS

Would you like to take part in a research study?

We are looking for young people (14 to 25 years old) who are experiencing mental health issues or concerned about their mental health to take part in a study.

This leaflet tells you more about the study. Please read it carefully and discuss it with others if you wish.

DO I HAVE TO TAKE PART IN THIS STUDY?

NO. It is completely up to you to decide whether you want to take part. If you decide not to take part, it will not affect the care which you will receive from your doctors. If you decide to take part and then change your mind, you can stop taking part in the study at any time without giving a reason.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

This study will help us to better understand the development of mental health disorders in adolescents and young people.

WHAT WILL HAPPEN IF I TAKE PART?

We will talk to you about the study.

- We can talk on the phone
- We would like to see you at the University of Birmingham, but can come to your home if necessary.

If you agree to take part then:

We will come and conduct assessments with you, lasting approximately 1 to 2 hours. We will ask questions about symptoms, personal history, life events and functioning. You will also be asked to give a saliva sample for measurement of genetics. You don't have to do this part if you don't want to.

You will be asked to complete these assessments again after 3, 6, 12, 18, and 24 months. At the end of each assessment, you will receive **£20** in recognition of your time and expenses.

WHAT ARE THE POSSIBLE RISKS OF TAKING PART IN THIS STUDY?

There are no known risks of taking part in this study. However, you do not have to answer anything that you do not feel comfortable with and you can stop at

WHAT WILL HAPPEN AFTER THE STUDY?

The results will be published in journal articles and presented at conferences. Your identity will never be revealed. We can send you a summary of the results at the end of the study.

IS TAKING PART CONFIDENTIAL?

YES. All information will be stored in a secure location. We will remove any contact details so that you will not be recognised from it. Only members of the research team will ever have access to this information.

TRAN🌀ITION🌀

Snapshot of the study

The purpose of the Transitions Study is to track the development of mental illnesses in young people through their natural course from first emergence, with the aim of identifying underlying vulnerability markers and modifiable risk factors. In the long run, the superior objective is to **develop and test a clinical staging model of mental health disorders** by means of clinical, psychological, social and genetic markers which could be implemented reliably in clinical services. We aim to recruit 500 participants from in the   , and follow them up periodically for at least 2 years.

Who is eligible and what would be involved?

We are looking for any young person aged 14 to 25 years who is seeking help at   for mental health issues. Participation will involve an interview and questionnaires about symptoms, personal history, life events and functioning. These would take place at the University of Birmingham or the participant's home at baseline and after 3, 6, 12, 18, and 24 months. We will reimburse young people £20 for each assessment in recognition of their time.

The only exclusion is an inability to consent because of lack of capacity or poor English language skills.

Your part

We ask your support in recruiting young people into the study. We appreciate that your time is very limited, but we ask that if you see a young person who fits our criteria, you refer them to us.
We hope to attend clinics. In this case, we will be available for you to introduce us to young people who are interested in participating at the end of their appointment.
If we are not at the clinic, young people can fill out the attached form to give us consent to contact them. If you could keep these forms, we will organise to collect them from you.
Young people can contact us directly using any of the contact details on the 'Letter to Participants' or information pamphlet.

We are very grateful for your support in recruitment, which is essential to the success of this study. If you have any questions, please contact   or

Many thanks,

The Transtitions Team

More information about the study and clinical staging…

The planned research program (the Transitions Study) will test a theoretical framework known as the 'clinical staging model', which defines the extent of a young person's mental illness along a continuum: starting with those who are at increased risk of a mental illness but are not yet showing symptoms then moving through to mild and then increasingly severe symptoms.

Clinical staging is a tool used to better individualise and tailor each young person's services and care. It allows interventions to be matched to the young person's illness course, characterising and monitoring:

- Vulnerability
- Early symptoms
- Established illness trajectory
- Recovery phase

To our knowledge, this concept has never been tested before on a large scale.

To better allow us to define the progression of any mental illness over time, we have proposed a clinical staging model for psychiatry, similar to that used in physical medicine. This type of staging framework is particularly useful since it organises clinical, psychosocial and biological data in a coherent fashion, and allows clinicians to determine where an individual lies on the continuum of the course of their illness. This can be used to guide the selection of treatments that are most appropriate to the specific stage of illness. Thus, more benign interventions can be chosen for those in the earlier stages of illness, leaving treatments that carry greater risk for those whose illness is long-standing and pervasive.

We will test the validity of a range of clinical, psychological, biological, genetic and social markers for their ability to define the individual's stage of illness and predict their risk of transition to a more advanced stage of illness. We are particularly interested in determining which of these markers represent modifiable risk factors and which represent the consequence of illness. We aim to use these data to further develop clinical staging criteria, so that staging of mental disorders can be implemented with reliability and validity, and finally, to use this cohort as a backbone for more specific studies of clinical staging, including testing stage-based interventions and more specialised neurobiological investigations of stage transitions.

TRANSITIONS

We are currently carrying out some research at the University of Birmingham and working with the ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ to find people interested in participating. The aim of this research is to better understand the development of mental health disorders in adolescents and young adults. We would like to invite you to take part in this study, which will include questions about different kinds of thoughts and feelings (that might or might not relate to you), your personal history and other aspects of your life. We will also ask you for a saliva sample for genetic analysis, although you don't have to do this part if you don't want to.

The first assessment will take around two hours, and we will pay you £20 for your time and travel expenses. After three, six, twelve, 18 and 24 months we will ask you again to take part in a shorter version of the assessment (taking around one hour) for which you will receive £20 each time.

If you would like to take part in this study, or if you would like more information about it before you decide, please contact us in one of these ways:

Call or text: ⬛⬛⬛⬛⬛⬛
Email: ⬛⬛⬛⬛⬛⬛⬛⬛
Facebook message: ⬛⬛⬛⬛⬛⬛

Another option is to fill out the form on the next page and leave it with your clinician and we will contact you.

We look forward to hearing from you!

Best wishes,

The Transition Team
(Research team at the University of Birmingham)

Put your name here

I, _____, agree to being contacted by the research team to discuss participation in the **Transitions Study**.

The best way to contact me is by:

Add your contact details here!

Email: _____

Telephone: _____

Put your signature here

Today's Date: _____

Your signature: _____

That's it– now just leave your form with your clinician and you'll hear from us soon!

TRANSITIONS

PARTICIPANT INFORMATION

Study Title: **The Transitions Study**

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

The purpose of the study:
This study aims to better understand the development of mental health disorders in adolescents and young people. We hope to assess young people presenting with mental health concerns over an extended period. This will hopefully tell us more about the relationships between mental health and other personal and lifestyle factors. We want to find out whether it helps people's treatment and recovery if we can classify the problems into recognisable stages.

Why have I been chosen?
We are inviting young people who are experiencing mental health issues to take part in this study. You have been asked because you sought help for these problems.

Do I have to take part?
No – involvement in this study is voluntary. If you decide to take part, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of health care you receive now or in the future.

What will happen to me if I take part?
The researcher will meet with you at the University of Birmingham, your home or at a health centre to carry out some assessments with you. These will consist of an interview and some questionnaires asking about different symptoms and feelings (that might or might not relate to you) and other aspects of your life and personal history. We will also ask you to give a saliva sample for genetic analysis, although you don't have to do this if you don't want to.

The first assessment will take approximately two hours to complete and you will receive **£20** in recognition of your time and expenses, upon completion of assessments. We will also make contact with you in three, six, twelve, 18 and 24 months time to complete a shorter assessment of about 60 minutes each. You will receive £20 each time.

We may invite you to take part in further related studies, such as the investigation of biological factors that may underlie mental health issues, for example brain imaging. You

will be paid for your time if deciding to participate in these add-on studies, which you don't have to do if you don't want to.

What are the possible side effects of taking part?
We do not expect that any part of this study will cause harm to anyone taking part in it. Some people might find it difficult discussing their symptoms, life events or other personal information. You don't have to answer anything that you are not comfortable with and you can stop at any time. If you experience distress and would like to discuss it with someone, we will organise this for you.

What are the possible benefits of taking part?
On a personal level, participants from previous studies have found that talking to a study researcher and sharing issues that might contribute to the mental health issues they are experiencing to be helpful. Although we cannot promise the study will help you, the information we get from this study may help other young people dealing with similar kinds of problems.

What will happen when the research study stops?
The data will be put into a database and analysed together with data from other participants who took part in the study. The results will be published in journal articles - your identity will never be revealed. We will ask you at your appointment if you would like to see the results of the study when it is finished.

Will my taking part in this study be kept confidential?
All information collected as part of this research will be kept in a locked filing cabinet and stored securely on a computer at University of Birmingham. We will give you an individual code, and all data from your interview will be stored using this code, not your name. Your GP or clinician may be informed of your participation, but only the research team will have access to your personal information. In the future, we may also send some of your data to colleagues in other universities, but we will never send information that could identify you. The data will be stored for a minimum of five year. All your information will be kept confidential, unless you tell us something that gives us reason to believe that you or others are in danger (e.g. having strong suicidal thoughts). In this event, we will talk with you about it before we share the information (e.g. telling your clinician).

What will happen to the results of the research study?
The results of the study will be written up for publication in health professional journals and will be presented at conferences in the UK and abroad. Your identity will never be revealed.

Who is organising and funding the research?
The research is sponsored by The University of Birmingham and is a PhD student project.

What if there is a problem?
If you are worried or concerned about any aspect of the study you should talk to the researcher. If they are unable to address your concerns or wish to make a complaint about the study, you can contact your local Patient Advice and Liaison Service - ; text ; email

Who has reviewed the study?
All research in the NHS is examined by an independent group of people called a Research Ethics Committee. Their job is to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the NRES Committee

Contact for Further Information
Please contact or Kareen Heinze (PhD Researcher) on or We are situated at School of Psychology, University of Birmingham.

If you agree to participate, you will be given a copy of this Information Sheet and a copy of the signed consent form to keep.

Thank you for reading this!

PARTICIPANT CONSENT FORM (16 years of age or older)

Study Title: The Transitions Study

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated May 2012 (version 2) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to my medical records from my GP and the	☐	☐
I give permission for researchers to inform my GP/clinician of my participation in the study.	☐	☐
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐
I give permission for researchers to provide my treating clinician/GP with a written summary of my scores from this assessment, where it is relevant to my treatment and care.	☐	☐
I agree: To participate in the interview and questionnaire part of this study.	☐	☐
To provide a saliva sample for genetic analyses.	☐	☐

To being contacted for follow-up assessments as part of the
ongoing study.

☐ ☐

To being contacted for participation in other studies related
to this one.

☐ ☐

_____   _____   _____
Name of Participant   Date   Signature

_____   _____   _____
Name of Person taking consent Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

TRANSITIONS

PARTICIPANT CONSENT FORM (younger than 16 years of age)

Study Title: The Transitions Study

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated May 2012 (version 2) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to my medical records from my GP and the ███████████ ██████████████████ .	☐	☐
I give permission for researchers to inform my GP/clinician of my participation in the study.	☐	☐
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐
I give permission for researchers to provide my treating clinician/GP with a written summary of my scores from this assessment, where it is relevant to my treatment and care.	☐	☐
I agree: To participate in the interview and questionnaire part of this study.	☐	☐
To provide a saliva sample for genetic analyses.	☐	☐
To being contacted for follow-up assessments as part of the ongoing study.	☐	☐

To being contacted for participation in other studies related to this one. ☐ ☐

_____ _____ _____
Name of Participant   Date   Signature

_____ _____ _____
Name of Parent/Guardian   Date   Signature

_____ _____ _____
Name of Person taking consent Date   Signature
(if different from researcher)

_____ _____ _____
Researcher   Date   Signature

TRANSITIONS

PARENT/GUARDIAN CONSENT FORM (for participants under 16 years)

Study Title: The Transitions Study

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated May 2012 (version 2) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that the participation of the child under my guardianship is voluntary and that he/she is free to withdraw at any time, without giving any reason, and without his/her medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to the medical records of the child under my guardianship from his/her GP and the	☐	☐
I give permission for researchers to inform the GP/clinician of the child under my guardianship of his/her participation in the study.	☐	☐
I understand that relevant sections of medical notes and data collected during the study may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to his/her taking part in this research. I give permission for these individuals to have access to his/her records.	☐	☐
I give permission for researchers to provide the treating clinician/GP of the child under my guardianship with a written summary of their scores from this assessment, where it is relevant to his/her treatment and care.	☐	☐

I agree for the child under my guardianship:
To participate in the interview and questionnaire part of this study. ☐ ☐

To provide a saliva sample for genetic analyses. ☐ ☐

To being contacted for follow-up assessments as part of the ongoing study. ☐ ☐

To being contacted for participation in other studies related to this one. ☐ ☐

_____   _____   _____
Name of Parent/Guardian   Date   Signature

_____   _____   _____
Name of Person taking consent Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

TRANSITIONS

Would you like to take part in research?

We are looking for young people (ages 14-25) to take part in a study about BRAIN DEVELOPMENT in mentally healthy adolescents and young adults at the University of Birmingham.

What does the research involve?
•Brain imaging (MRI) session
•Hormone analysis by means of a small hair sample
•Interview about hair-related factors (e.g. hair colour) and questions about mental health
•Assessments take between **1-2 hours**
•You will receive **£20** and we offer you a free disk with the pictures of your brain

WANT TO KNOW MORE?

➢ call or text us:
➢ email us on
➢ Facebook message us:

TRANSITIONS

Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

We are writing to invite you to take part in an extra study that is related to your participation in the Transitions Study. The aim of this research is to investigate the role of neurobiological factors that underlie mental health issues in adolescents and young people. Taking part in this research will involve brain imaging (Magnetic Resonance Imaging, MRI) and hormone analysis, which we do by taking hair samples (please find a detailed description in the enclosed Participant Information Sheet).

The assessment will take around **one and a half hours**, and we will pay you **£20** for your time and travel expenses. After six months we will ask you again to take part in the same assessment, and after 12 months we will ask you for a hair sample and to answer some questions. We will give you additional £20 for completing the assessment after six months and another £5 after completing the assessment after 12 months. If you only want to take part in either the MRI study or the hair hormone study, we would reimburse you separately with £15 for the MRI study and £5 for the hair hormone study at the first and second assessment.

If you would like to take part in this study, or if you would like more information about it before you decide, please contact us in one of these ways:

Call or text us:
Email us:
Facebook message us:

We look forward to hearing from you!

Best wishes,

Kareen & the Transition Team

TRANS**ITION**S

Neurobiological Markers of Risk for Mental Health Issues – First follow-up study
(The Transitions Study)

We are writing to invite you to a follow-up study that is related to your participation in the brain imaging (Magnetic Resonance Imaging, MRI) and hair hormone study. The aim of this research is to investigate the role of neurobiological factors that underlie mental health issues in adolescents and young people over an extended period of time. Taking part in this research will involve the same assessment that you did six months ago, in which you had a brain scan and gave a sample of hair.

The assessment will take around **one and a half hours**, and we will pay you **£20** for your time and travel expenses. If you only want to take part in either the MRI study or the hair hormone study, we would reimburse you separately with £15 for the MRI study and £5 for the hair hormone study.

If you would like to take part in this study, or if you would like more information about it before you decide, please contact us in one of these ways:

Call or text us:
Email us:
Facebook message us:

We look forward to hearing from you!

Best wishes,

Kareen & the Transition Team

TRAN**S**ITION**S**

PARTICIPANT INFORMATION

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

The purpose of the study
This study will investigate the role of different hormones (such as cortisol, cortisone, testosterone) and the structure and function of the brain in the development of mental health issues. We want to find out whether there are any identifiable brain or hormonal factors that contribute to mental health issues and if they help to classify mental problems into recognisable stages.

Why have I been chosen?
We are inviting young people who are taking part in the Transitions Study and who are experiencing mental health issues which persist for more than 6 weeks and/or have a family member with mental health issues, to participate in this study.

Do I have to take part?
No – involvement in this study is voluntary. If you decide to take part, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of health care you receive now or in the future.

What will happen to me if I take part?
You will undergo an Magnetic Resonance Imaging scan (please find information below) and you will be asked to give a small hair sample from the back of your head and answer some questions that are relevant for the hair hormone analysis.

Magnetic resonance imaging (MRI) is a way to take pictures of the inside of the body, and for this study, specifically of your brain. The process uses intense magnetic fields and radio waves to create these images. We will get information about both the structure and function of your brain. You will be asked to go through a safety questionnaire with a scan operator before being allowed into the scanner itself.

You will be asked to lie completely still on your back while the machine will surround the upper part of your body. The scanning session will last around 45 minutes during which there will be times when you have to do some tasks while looking at a screen, and times when you will be asked to let your mind wander freely.

The full assessment will take around one and a half hours, and we will pay you £20 for your time and travel expenses for both parts of the study. If you only feel happy to take part in one assessment, we will offer you £15 for the scanning session and £5 for the hair hormone analysis.

What are the possible benefits of taking part?
It is unlikely that there will be any direct benefits to you from taking part. However, we hope that this study will help us understand the development of mental health issues, and give us some idea of whether there are 'stages' to these illness that can be separated by looking at brain scans or hormone measures. If we can do this, it may help us to select the best treatment for a person's stage of illness.

What are the possible side effects of taking part?
The MRI procedure is considered to be extremely safe and non-invasive. However, the scanner is noisy so all participants will wear earplugs and headphones. The MRI is a small space and can cause distress for people who are afraid of small places. If you think you may feel claustrophobic, please discuss this with us and we can do a practice run in a mock scanner. If this is uncomfortable for you, we don't need to proceed.

The main risks of MRI are because of people taking metal objects into the scanning room. This is particularly dangerous if you have metal in your body from surgery (for example a pacemaker), or from an accident (such as having metal filings in your eye from welding or grinding metal). We will ask you questions about this, and it is important for you to tell us if there is a chance you have metal in you.

You will be carefully introduced to the scanner and you are allowed to leave at any stage. While lying motionless on the scanner bed, you may experience back and neck pain. This will be minimized by the use of comfortable padding and positioning.

There is no known extra risk in conducting MRI scans on women who are pregnant. However, it is conventional to exclude women who are pregnant from research using MRI scans. A pregnancy test kit will be available, should women wish to use it before undergoing a scan.

Whilst in the scanner, you can talk to the operator at any time and will be holding an emergency button which you can squeeze during a scan in the event of distress. This will activate an alarm and cause the operator to immediately stop the scan.

What will happen when the research study stops?
The results will be written up for scientific publication. All data will be reported anonymously.

Will my taking part in this study be kept confidential?
All information collected as part of this research will be kept in a locked filing cabinet and stored securely on a computer at University of Birmingham. We will give you an individual code, and all data from your interview will be stored using this code, not your name. Your GP or clinician may be informed of your participation, but only the research team have access to your personal information. The data will be stored for a minimum of five years. All your information will be kept confidential, unless you tell us something that gives us reason to believe that you or others are in danger (e.g. having strong suicidal thoughts). In this event, we will talk with you about it before we share the information (e.g. telling your clinician).

What will happen to the results of the research study?
The results of the study will be written up for publication in health professional journals and will be presented at conferences in the UK and abroad. Your identity will never be revealed.

Who is organising and funding the research?
The research is being undertaken as part of a PhD at the University of Birmingham.

What if there is a problem?
If you are worried or concerned about any aspect of the study you should talk to the researcher. If they are unable to address your concerns or wish to make a complaint about the study, you can contact your local Patient Advice and Liaison Service - ; text ; email

Who has reviewed the study?
All research in the NHS is examined by an independent group of people called a Research Ethics Committee. Their job is to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the NRES Committee .

Contact for Further Information
Please contact Kareen Heinze (PhD Researcher) on or We are situated at School of Psychology, University of Birmingham.

If you agree to participate, you will be given a copy of this Information Sheet and a copy of the signed consent form to keep.

Thank you for reading this.

TRANSITIONS

PARTICIPANT CONSENT FORM (16 years of age or older)

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to my medical records from my GP and the	☐	☐
I give permission for researchers to inform my GP/clinician of my participation in the study.	☐	☐
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐

I agree:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To do the magnetic resonance imaging session.	☐	☐
To give a hair sample for hormone analysis.	☐	☐
To being contacted for participation in other studies related to this one.	☐	☐

_____   _____   _____
Name of Participant   Date   Signature

_____   _____   _____
Name of Person taking consent Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

TRANSITIONS

PARTICIPANT CONSENT FORM (younger than 16 years)

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to my medical records from my GP and the	☐	☐
I give permission for researchers to inform my GP/clinician of my participation in the study.	☐	☐
I understand that relevant sections of my medical notes and data collected during the study,may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐

I agree:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To give a hair sample for hormone analysis.	☐	☐
To being contacted for participation in other studies related to this one.	☐	☐

_____   _____   _____

Name of Parent/Guardian   Date   Signature

_____   _____   _____

Name of Participant   Date   Signature

_____   _____   _____

Name of Person taking consent   Date   Signature
(if different from researcher)

_____   _____   _____

Researcher   Date   Signature

TRANSITIONS

PARENT/GUARDIAN CONSENT FORM

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that the participation of the child under my guardianship is voluntary and that he/she is free to withdraw at any time, without giving any reason, and without his/her medical care or legal rights being affected.	☐	☐
I give permission for researchers on this study to access to the medical records of the child under my guardianship from his/her GP and the	☐	☐
I give permission for researchers to inform the GP/clinician of the child under my guardianship of his/her participation in the study.	☐	☐
I understand that relevant sections of medical notes and data collected during the study may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to his/her taking part in this research. I give permission for these individuals to have access to his/her records.	☐	☐

I agree for the child under my guardianship:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To do the magnetic resonance imaging session (only if child is over 16 years of age).	☐	☐

To give a hair sample for hormone analysis. ☐ ☐

To being contacted for participation in other studies related to this one. ☐ ☐

_____ _____ _____
Name of Parent/Guardian   Date   Signature

_____ _____ _____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____ _____ _____
Researcher   Date   Signature

TRANSITIONS

PARTICIPANT INFORMATION

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

The purpose of the study
This study will investigate the role of different hormones (such as cortisol, cortisone, testosterone) and the structure and function of the brain in the development of mental health issues. We want to find out whether there are any identifiable brain or hormonal factors that contribute to mental health issues and if they help to classify mental problems into recognisable stages.

Why have I been chosen?
We are inviting healthy, young people to take part in this study. Your data, as a control participant, will be compared to young people who sought help for mental health issues.

Do I have to take part?
No – involvement in this study is voluntary. If you decide to take part, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of health care you receive now or in the future.

What will happen to me if I take part?
You will undergo a Magnetic Resonance Imaging scan (please find information below) and you will be asked to give a small hair sample from the back of your head and answer some questions that are relevant for the hair hormone analysis.

Magnetic resonance imaging (MRI) is a way to take pictures of the inside of the body, and for this study, specifically of your brain. The process uses intense magnetic fields and radio waves to create these images. We will get information about both the structure and function of your brain. You will be asked to go through a safety questionnaire with a scan operator before being allowed into the scanner itself.

You will be asked to lie completely still on your back while the machine will surround the upper part of your body. The scanning session will last around 45 minutes during which there will be times when you have to do some tasks while looking at a screen, and times when you will be asked to let your mind wander freely.

The full assessment will take around one and a half hours, and we will pay you £20 for your time and travel expenses for both parts of the study. If you only feel happy to take part in one assessment, we will offer you £15 for the scanning session and £5 for the hair hormone analysis.

What are the possible benefits of taking part?
It is very unlikely that there will be any direct benefits to you from taking part. However, we hope that this study will help us understand the development of mental health issues, and give us some idea of whether there are 'stages' to these illness that can be separated by looking at brain scans or hormone measures. If we can do this, it may help us to select the best treatment for a person's stage of illness.

What are the possible side effects of taking part?
The MRI procedure is considered to be extremely safe and non-invasive. However, the scanner is noisy so all participants will wear earplugs and headphones. The MRI is a small space and can cause distress for people who are afraid of small places. If you think you may feel claustrophobic, please discuss this with us and we can do a practice run in a mock scanner. If this is uncomfortable for you, we don't need to proceed.

The main risks of MRI are because of people taking metal objects into the scanning room. This is particularly dangerous if you have metal in your body from surgery (for example a pacemaker), or from an accident (such as having metal filings in your eye from welding or grinding metal). We will ask you questions about this, and it is important for you to tell us if there is a chance you have metal in you.

You will be carefully introduced to the scanner and you are allowed to leave at any stage. While lying motionless on the scanner bed, you may experience back and neck pain. This will be minimized by the use of comfortable padding and positioning.

There is no known extra risk in conducting MRI scans on women who are pregnant. However, it is conventional to exclude women who are pregnant from research using MRI scans. A pregnancy test kit will be available, should women wish to use it before undergoing a scan.

Whilst in the scanner, you can talk to the operator at any time and will be holding an emergency button which you can squeeze during a scan in the event of distress. This will activate an alarm and cause the operator to immediately stop the scan.

What will happen when the research study stops?

The results will be written up for scientific publication. All data will be reported anonymously.

Will my taking part in this study be kept confidential?
All information collected as part of this research will be kept in a locked filing cabinet and stored securely on a computer at University of Birmingham. We will give you an individual code, and all data from your interview will be stored using this code, not your name. The data will be stored for a minimum of five years. All your information will be kept confidential, unless you tell us something that gives us reason to believe that you or others are in danger (e.g. having strong suicidal thoughts). In this event, we will talk with you about it before we share the information.

What will happen to the results of the research study?
The results of the study will be written up for publication in health professional journals and will be presented at conferences in the UK and abroad. Your identity will never be revealed.

Who is organising and funding the research?
The research is being undertaken as part of a PhD at the University of Birmingham.

What if there is a problem?
If you are worried or concerned about any aspect of the study you should talk to the researcher. If they are unable to address your concerns or wish to make a complaint about the study, you can contact your local Patient Advice and Liaison Service - call ⬛⬛⬛⬛⬛⬛⬛; text ⬛⬛⬛⬛⬛⬛; email ⬛⬛⬛⬛⬛⬛⬛⬛⬛.

Who has reviewed the study?
All research in the NHS is examined by an independent group of people called a Research Ethics Committee. Their job is to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the NRES Committee ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛.

Contact for Further Information
Please contact Kareen Heinze (PhD Researcher) on ⬛⬛⬛⬛⬛⬛⬛ or ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛. We are situated at School of Psychology, University of Birmingham.

If you agree to participate, you will be given a copy of this Information Sheet and a copy of the signed consent form to keep.

Thank you for reading this.

TRANSITIONS

PARTICIPANT CONSENT FORM (16 years of age or older)

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected.	☐	☐
I understand that relevant sections of data collected during the study, may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐

I agree:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To do the magnetic resonance imaging session.	☐	☐
To give a hair sample for hormone analysis.	☐	☐
To being contacted for participation in other studies related to this one.	☐	☐

_____   _____   _____
Name of Participant   Date   Signature

_____   _____   _____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   A-33   Signature

TRANSITIONS

A-34

PARTICIPANT CONSENT FORM (younger than 16 years)

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected.	☐	☐
I understand that relevant sections of data collected during the study, may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐	☐

I agree:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To give a hair sample for hormone analysis.	☐	☐
To being contacted for participation in other studies related to this one.	☐	☐

_____   _____   _____
Name of Parent/Guardian   Date   Signature

_____   _____   _____
Name of Participant   Date   Signature

_____   _____   _____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

TRANSITIONS

PARENT/GUARDIAN CONSENT FORM

Study Title: Neurobiological Markers of Risk for Mental Health Issues (The Transitions Study)

Name of Researcher:

	Yes	No
I confirm that I have read and understand the information sheet dated June 2012 (version 1) for the above study and have had the opportunity to ask questions.	☐	☐
I understand that the participation of the child under my guardianship is voluntary and that he/she is free to withdraw at any time, without giving any reason, and without his/her legal rights being affected.	☐	☐
I understand that relevant sections data collected during the study may be looked at by individuals from the University of Birmingham, from regular authorities or from the NHS Trust, where it is relevant to his/her taking part in this research. I give permission for these individuals to have access to his/her records.	☐	☐

I agree for the child under my guardianship:

	Yes	No
To participate in the interview and questionnaire part of this study.	☐	☐
To do the magnetic resonance imaging session (only if child is over 16 years of age).	☐	☐
To give a hair sample for hormone analysis.	☐	☐
To being contacted for participation in other studies related to this one.	☐	☐

_____   _____   _____
Name of Parent/Guardian   Date   Signature

_____   _____   _____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

Tracking Information

Full name (include middle)	
Mobile number	
Home number	
Home address (include postcode)	
Email address	
Facebook	Yes No username:
Name and contact of GP/health professional	
Full name of Mother (include middle)	
Full name of Father (include middle)	

Name and contact details of a person who may know how to get in contact with you.

Full name (include middle)		**Mobile #**	
Relationship to young person		**Home #**	
Home address		**Email address**	

Health services use

What is/are the main mental health problem(s) for which you went to see your GP? Have you been given a diagnosis?

_____
_____
_____
_____
_____
_____
_____

Depression ☐
Generalised Anxiety ☐
Panic Disorder ☐
PTSD ☐
Psychosis ☐
Eating Disorder ☐
Drug and alcohol ☐
ADHD ☐

Are there any other mental health issues you are struggling with at the moment or in the past?
(diagnoses, when did it start/end, medication or other treatments, etc.)

_____
_____
_____
_____
_____

When did your current problem(s) start? *(How old were you?)*

_____
_____
_____

When and where did you start seeking treatment for the current issues? *(overview of treatment history for current issues; details of prior treatment)*

_____
_____
_____
_____
_____
_____

What treatment are you receiving at the moment?

_____
_____
_____
_____
_____

Medication ☐
Psychotherapy, *if known, type (e.g.CBT):* _____ ☐
Counselling ☐
Other (e.g. priest): _____ ☐

Are you receiving any other kind of help or support *(e.g. information about mental illness, its treatment, and available services; help to sort out housing/money problems, to improve ability to work/use time in other ways or to look after yourself or home, or to meet other people for support and company)*

    Yes   ☐   No ☐

If yes, details:

_____

_____

_____

If receiving medication at the moment (e.g. antidepressants, neuroleptics, fish oil, vitamins etc.):

Name: _____

Type *(if other than tablets)*: _____

Dose: _____

Date commenced: _____

Duration classification:

Less than 1 month   ☐

1 to 3 months   ☐

3 to 6 months   ☐

More than 6 months ☐

If more than one, take notes here:

_____

_____

_____

_____

If applicable: prior medication, dose and when commenced/ended or if changes in dose of present medication:

_____

_____

_____

_____

Do you usually take your medication according to the recommended dose*?*

    Yes ☐

    No ☐

*Comments:*_____

Did you see the following professionals for mental health in the past 12 months?

    ☐ GP   ___ times

    ☐ Counsellor   ___ times

    ☐ Psychiatrist   ___ times

    ☐ Psychologist   ___ times

    ☐ Care coordinator/CPN   ___ times

    ☐ Other mental health professional: _____   ___ times

    ☐ Other non-mental health professional: _____   ___ times

In the past 12 months, were you / did you:

- ☐ admitted overnight or longer to any hospital for problems with your mental health *(such as stress, anxiety, depression, self harm or dependence on alcohol or drugs)?*____ times
- ☐ had a consultation with a professional for physical health? ____ times
- ☐ use the internet for mental health concerns? ____ times
- ☐ use a self-help group for problems with your mental health? ____ times
- ☐ use a telephone counselling service for problems with your mental health?____ times

What self management strategies have you used in the past year to cope with mental health problems?

_____
_____

- ☐ Increased level of exercise or physical activity
- ☐ Did more of the things enjoyed
- ☐ Sought support from family or friends
- ☐ Used alcohol or drugs
- ☐ Cut out alcohol or drugs

Family history of Psychological Disorders

Has your biological mother, father, brother(s) or sister(s) had a serious psychological or emotional problem? *(This refers to conditions such as depression, severe anxiety, nervous breakdown and schizophrenia)*
☐ Yes ☐ No

	Problem	Diagnosed?	Treatment/ Hospitalisation?	Suicide?
Mother				
Father				
Brother(s)				
Sister(s)				

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (CLINICIAN-RATED)

B-9

B-10

ASSIST

ASSIST

B-13

B-14

CAARMS

B-15

B-17

B-19

B-21

B-22

B-25

B-26

B-28

B-30
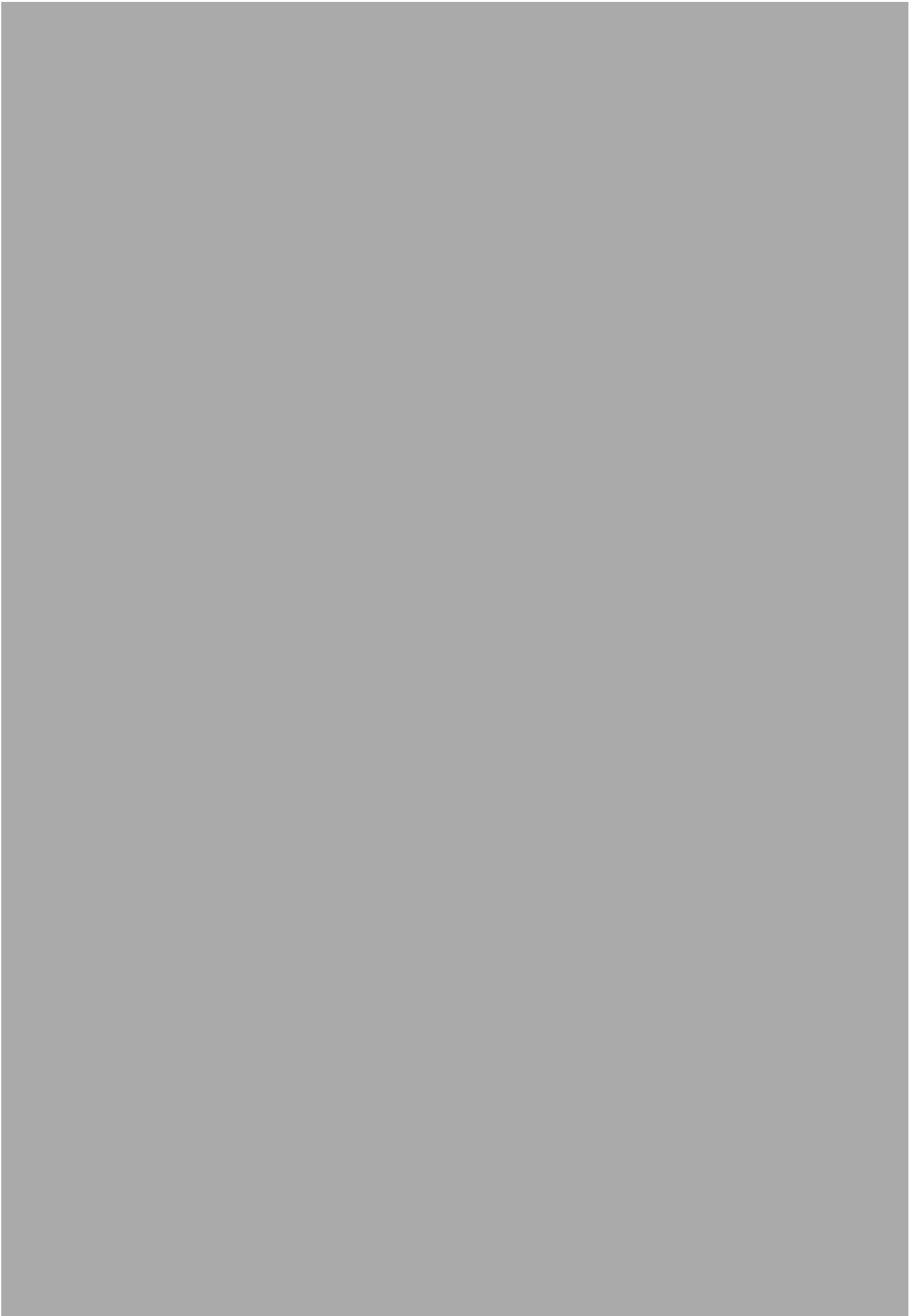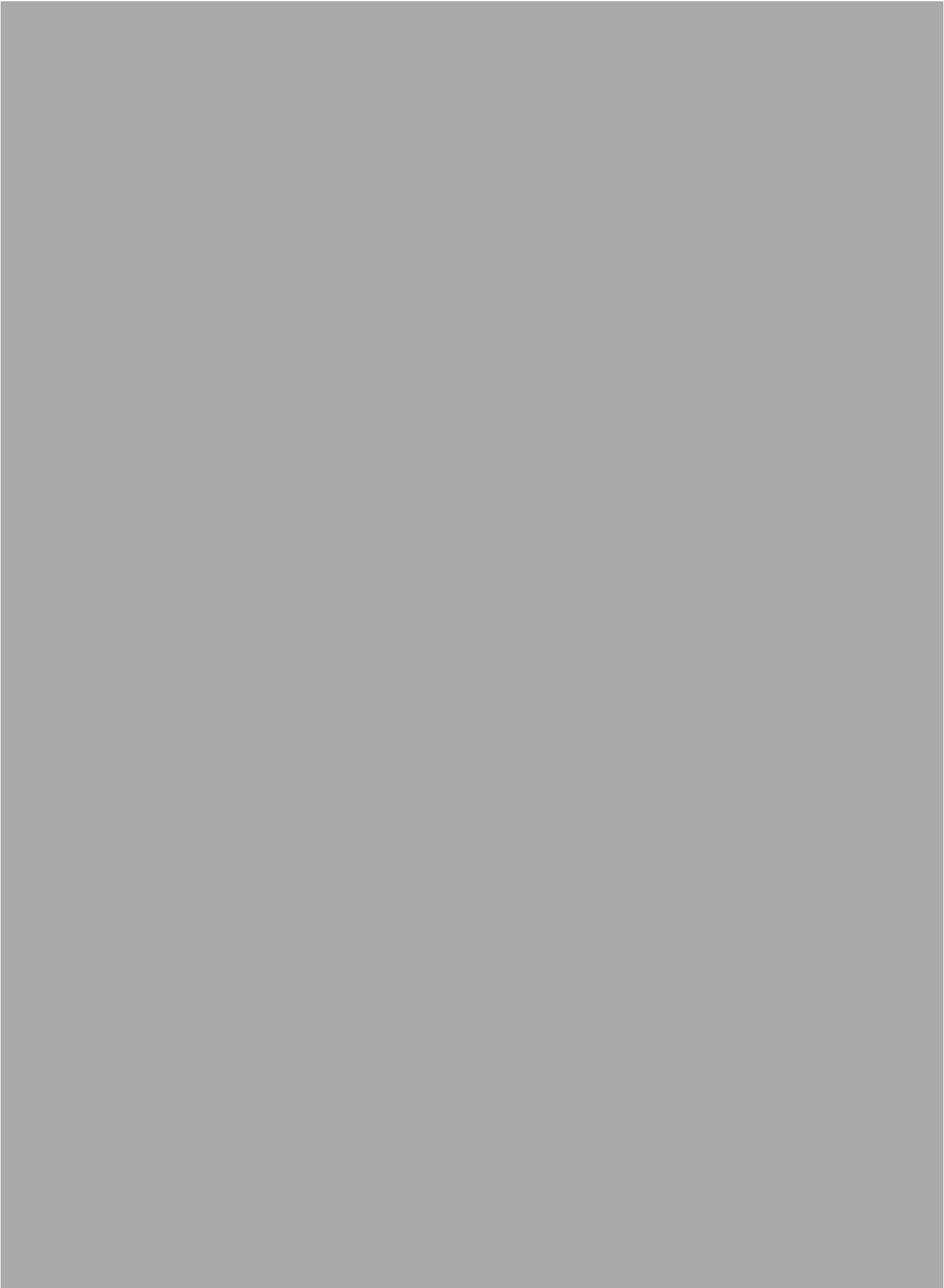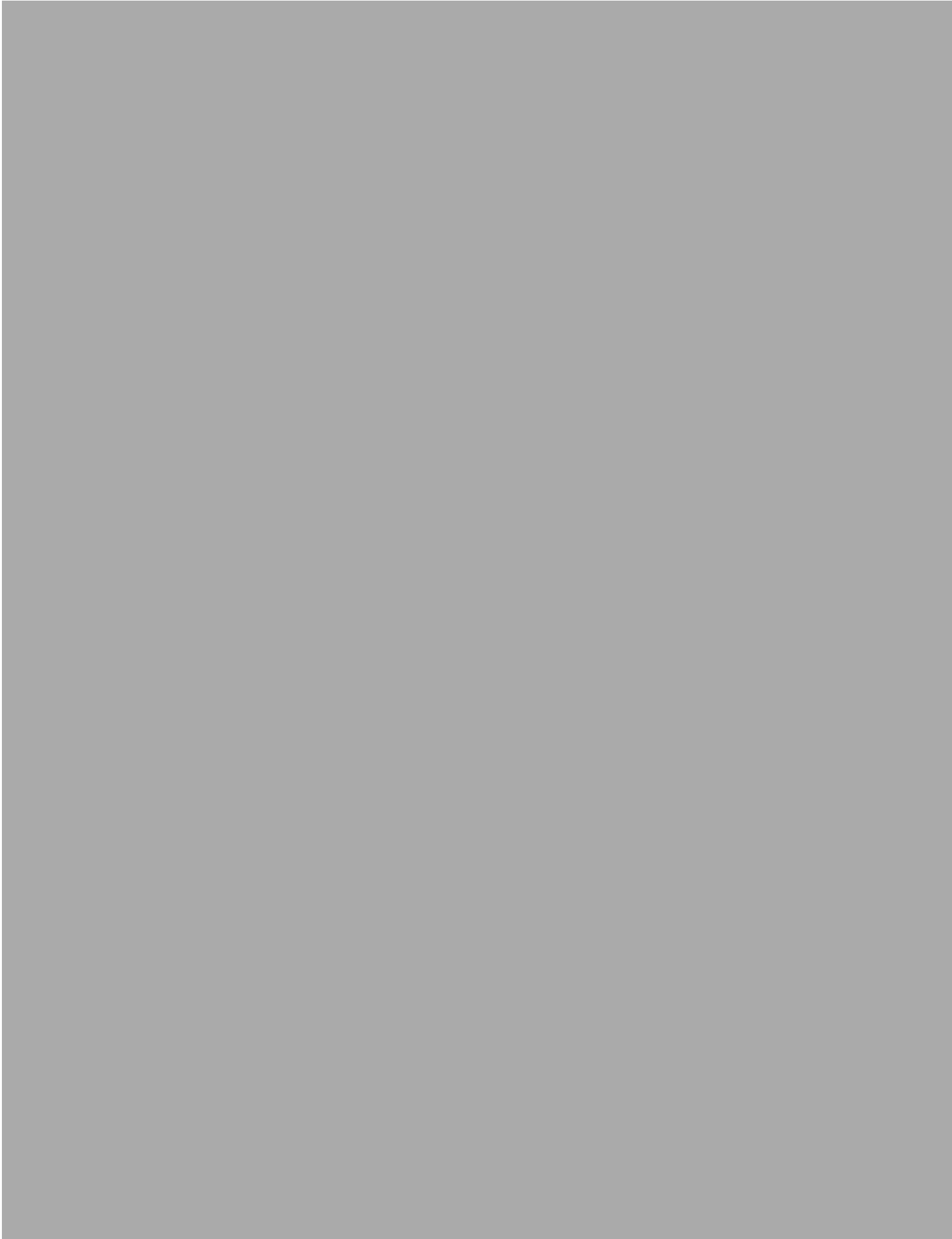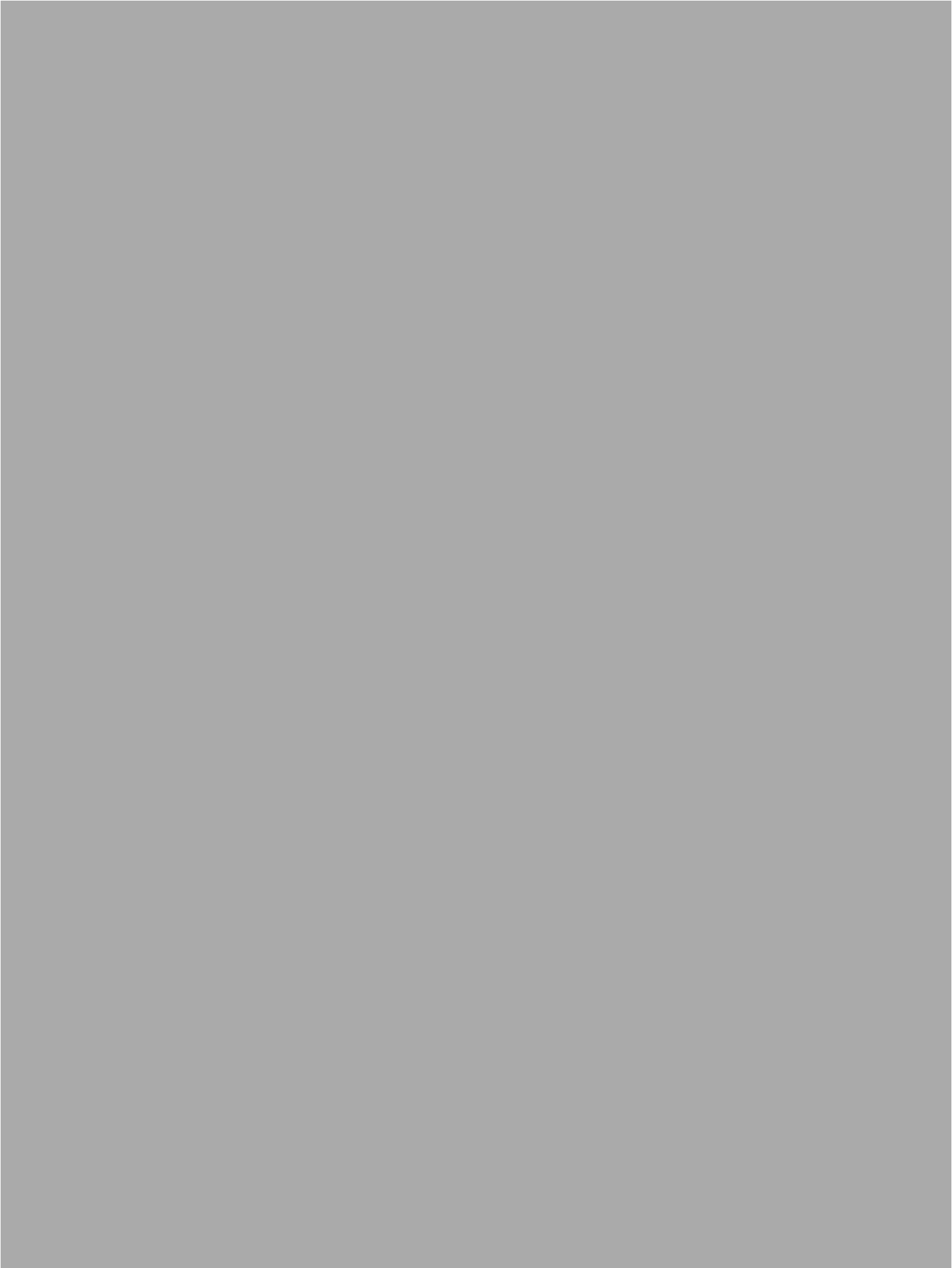
Physical measurements

Height: _____cm

Weight: _____kg

B-32

B-33

B-34

B-35

B-36

CTQ

CTQ

B-38

B-39

OVERALL ANXIETY SEVERITY AND IMPAIRMENT SCALE (OASIS)

B-40

B-41

B-42

B-43

B-44

B-46

B-47

B-51

B-52

B-54

B-55

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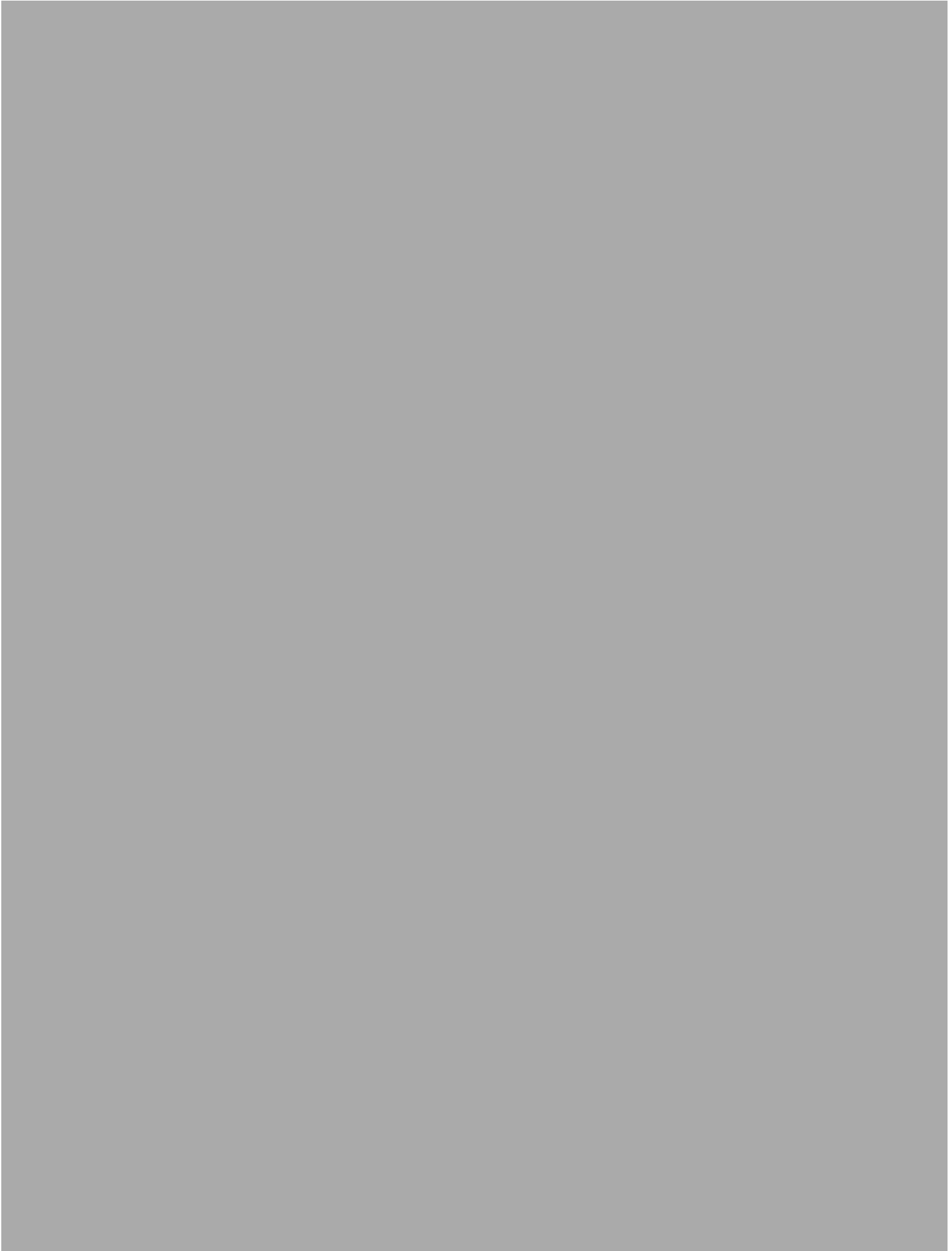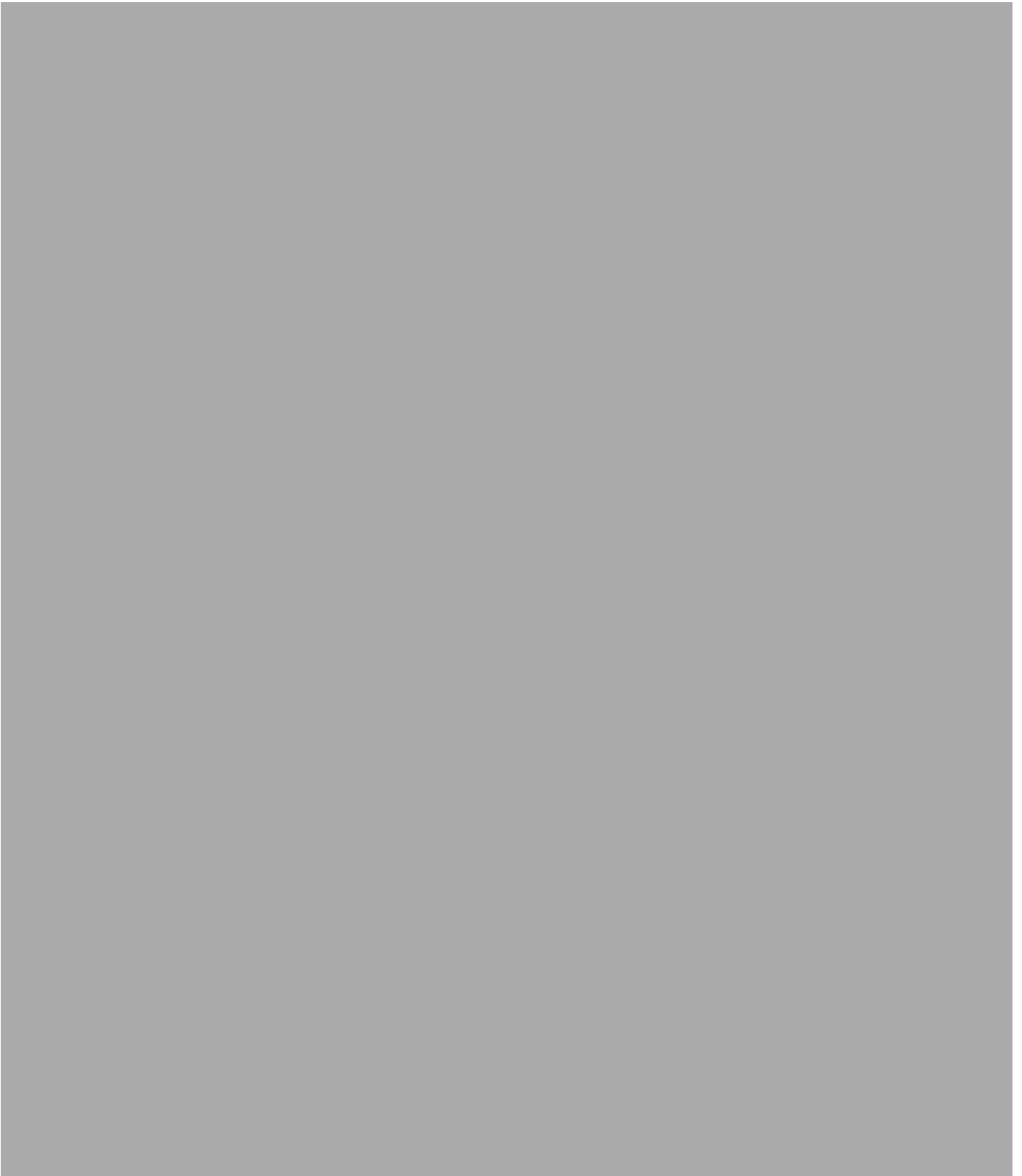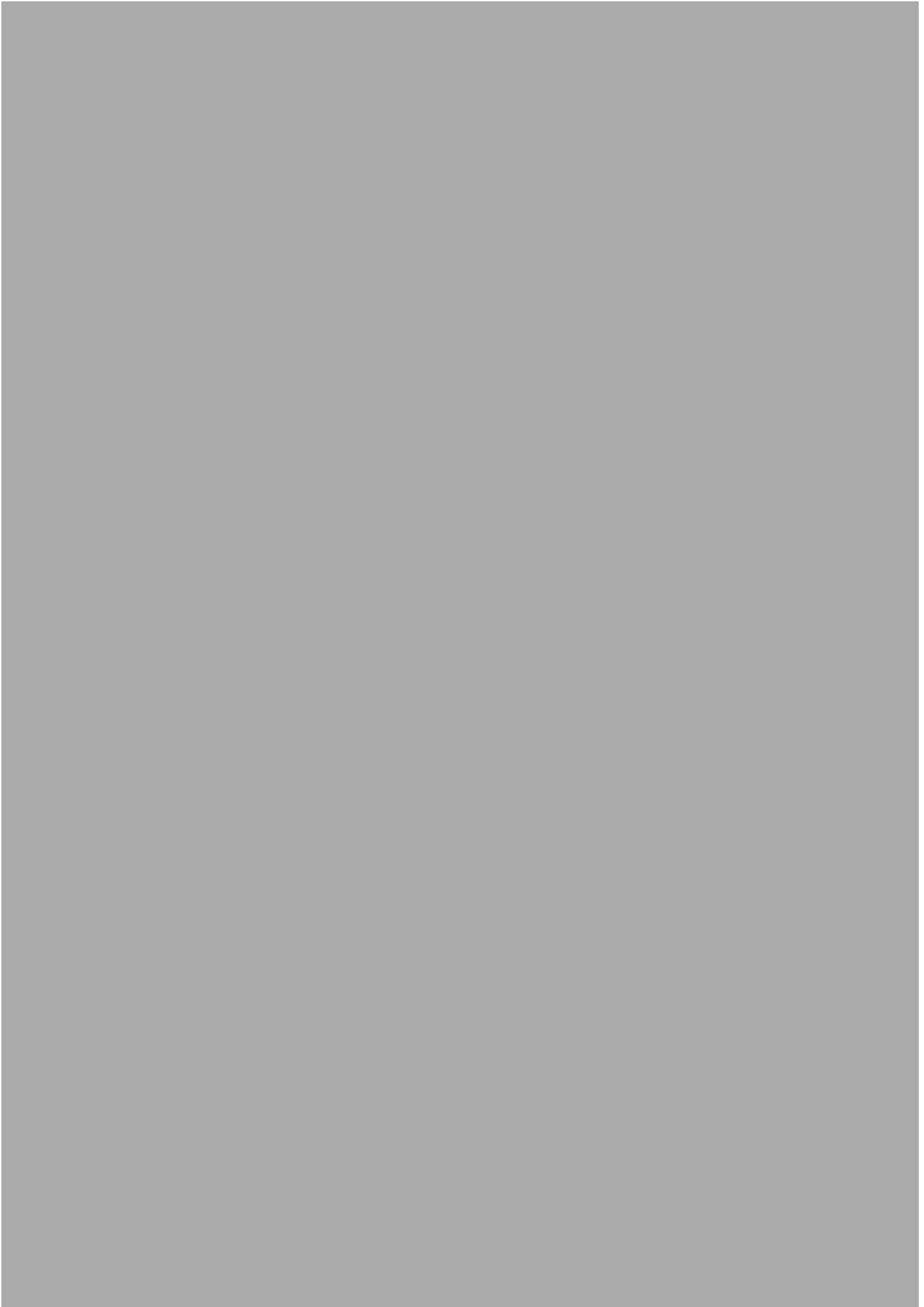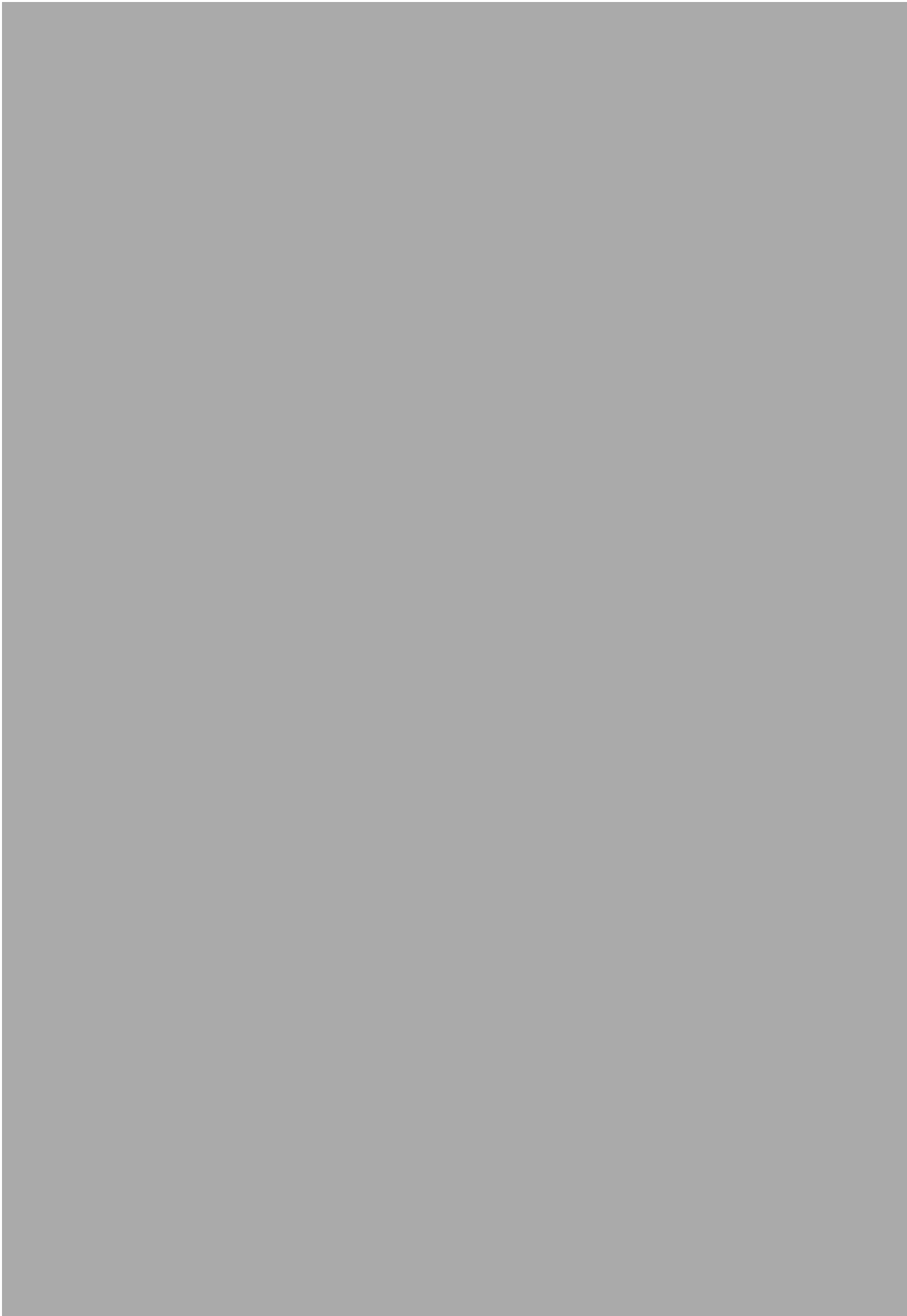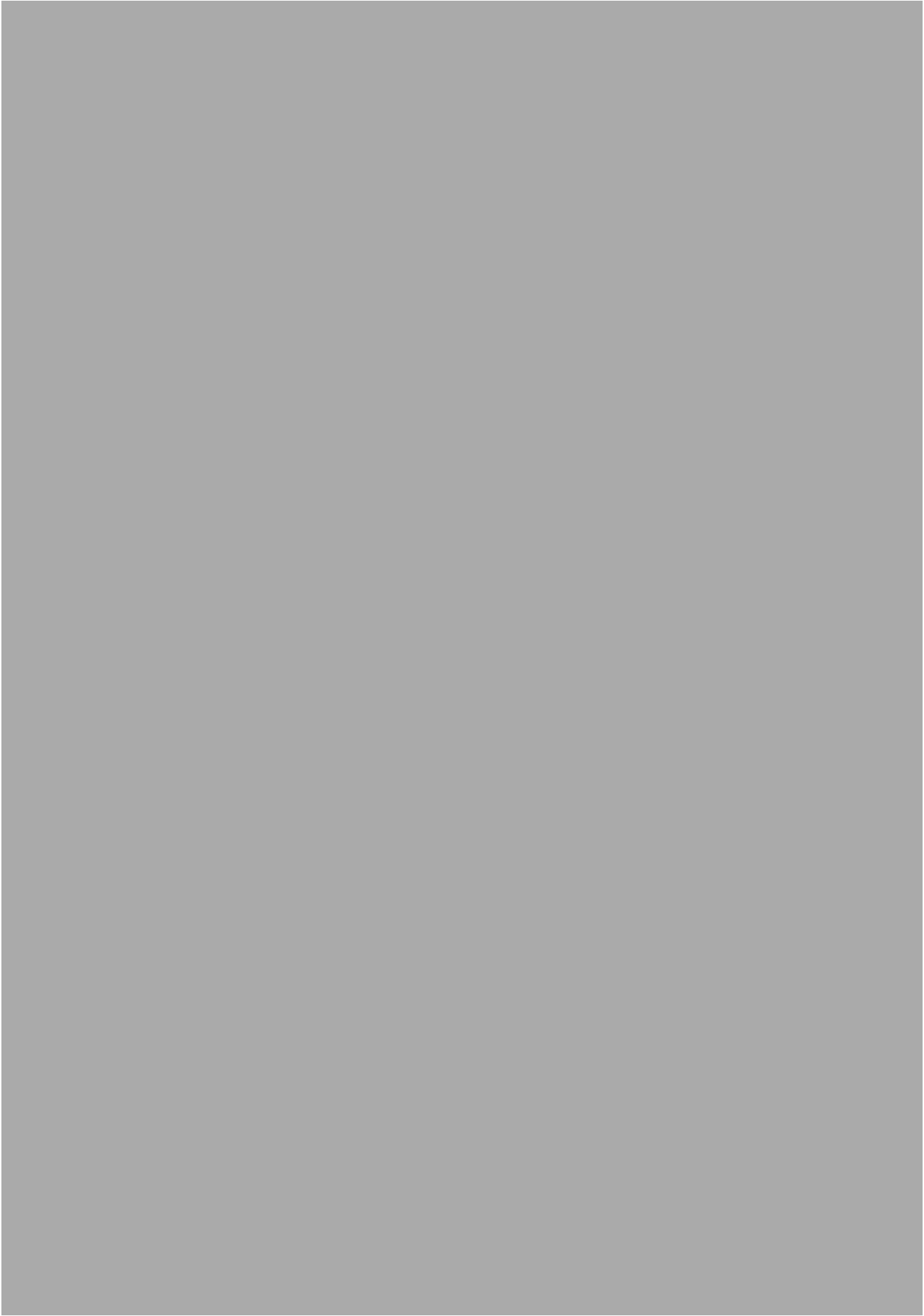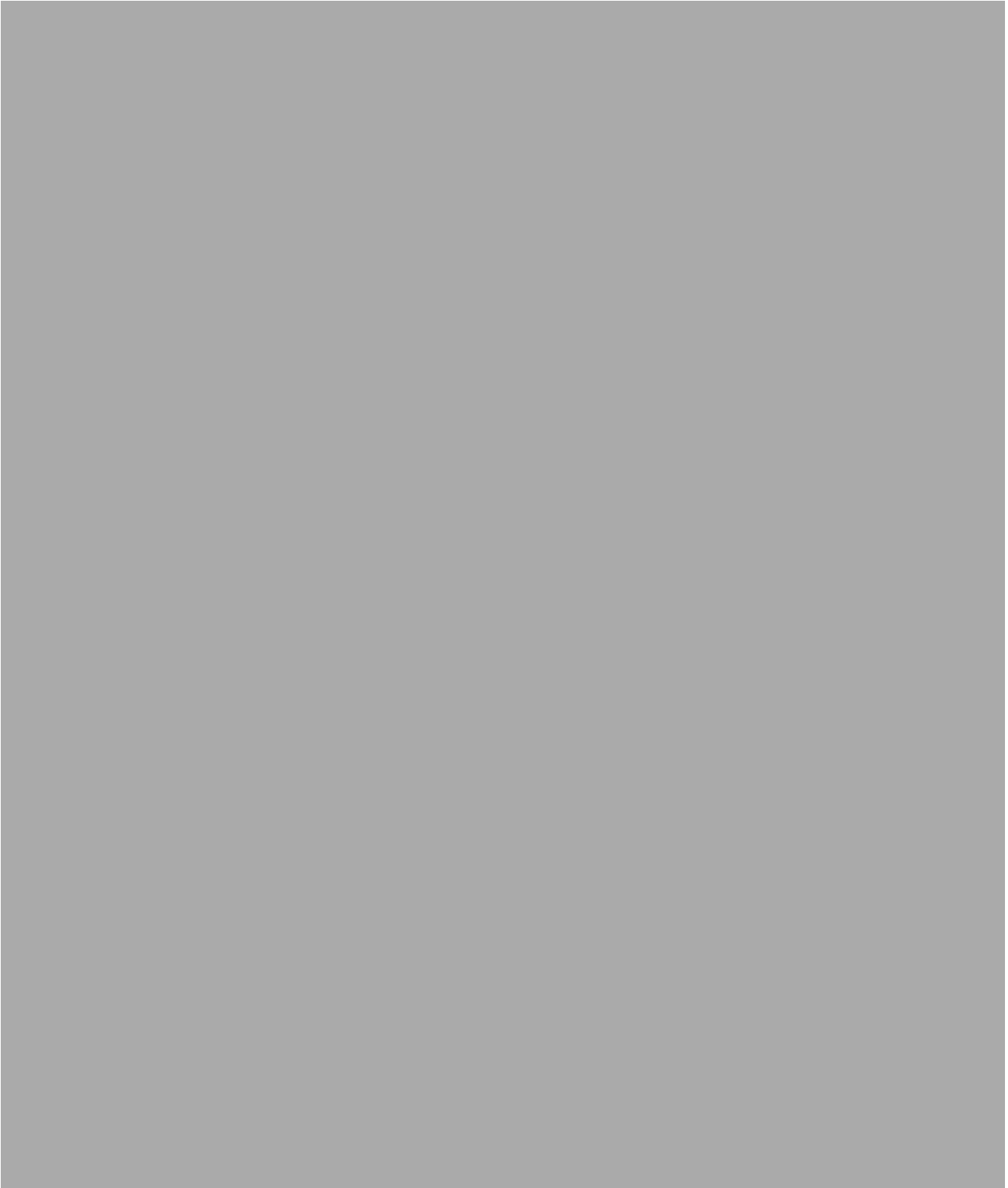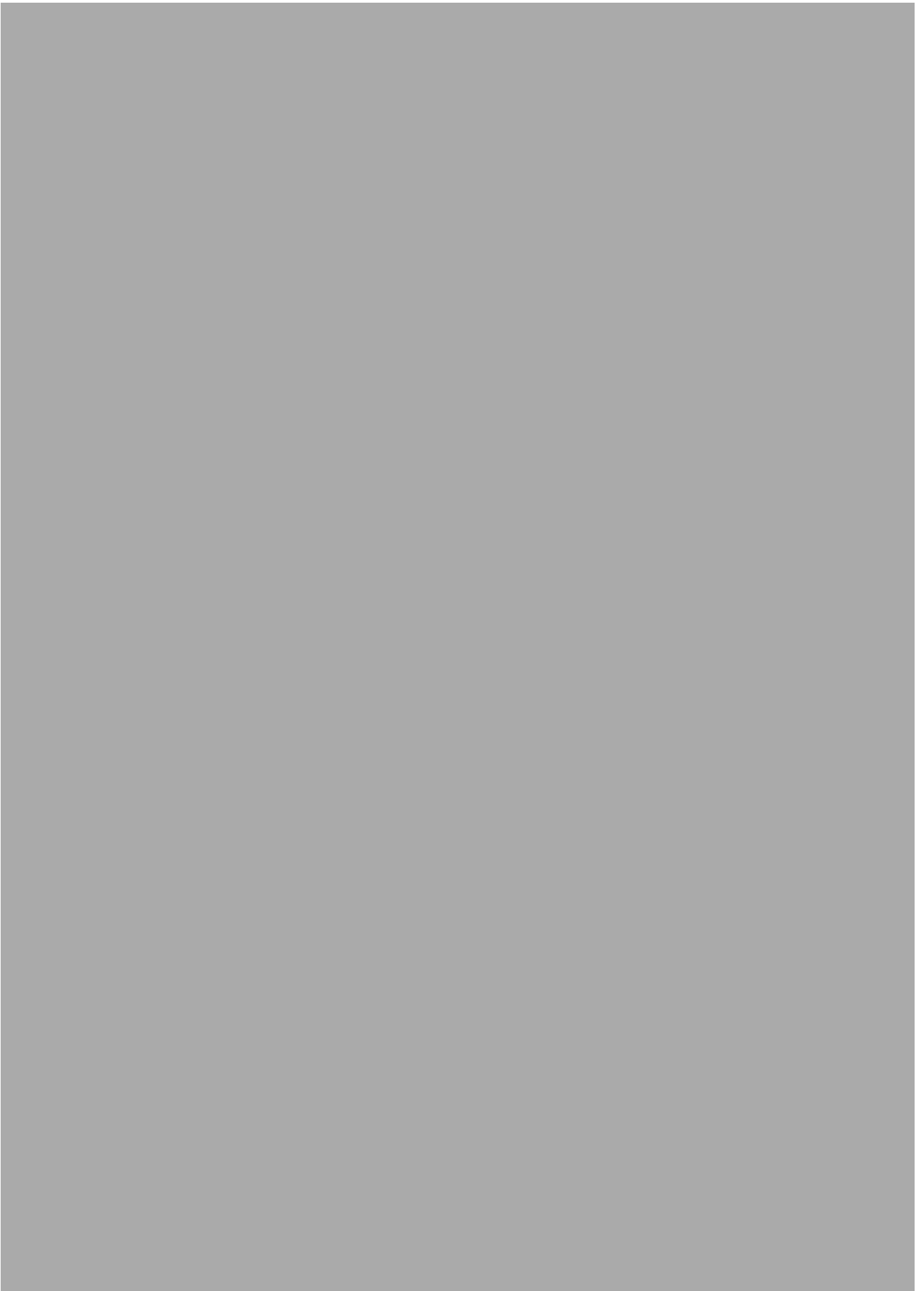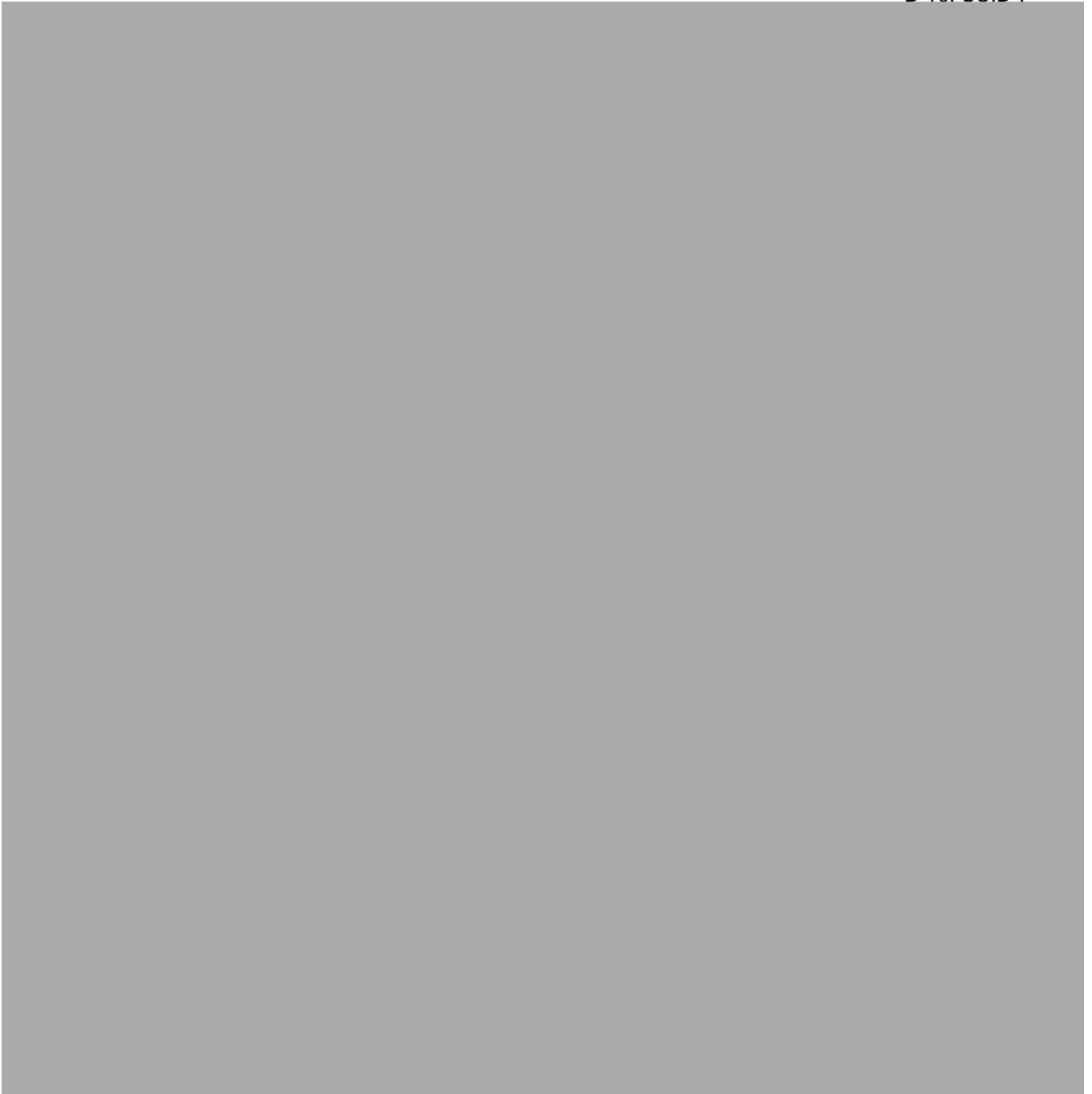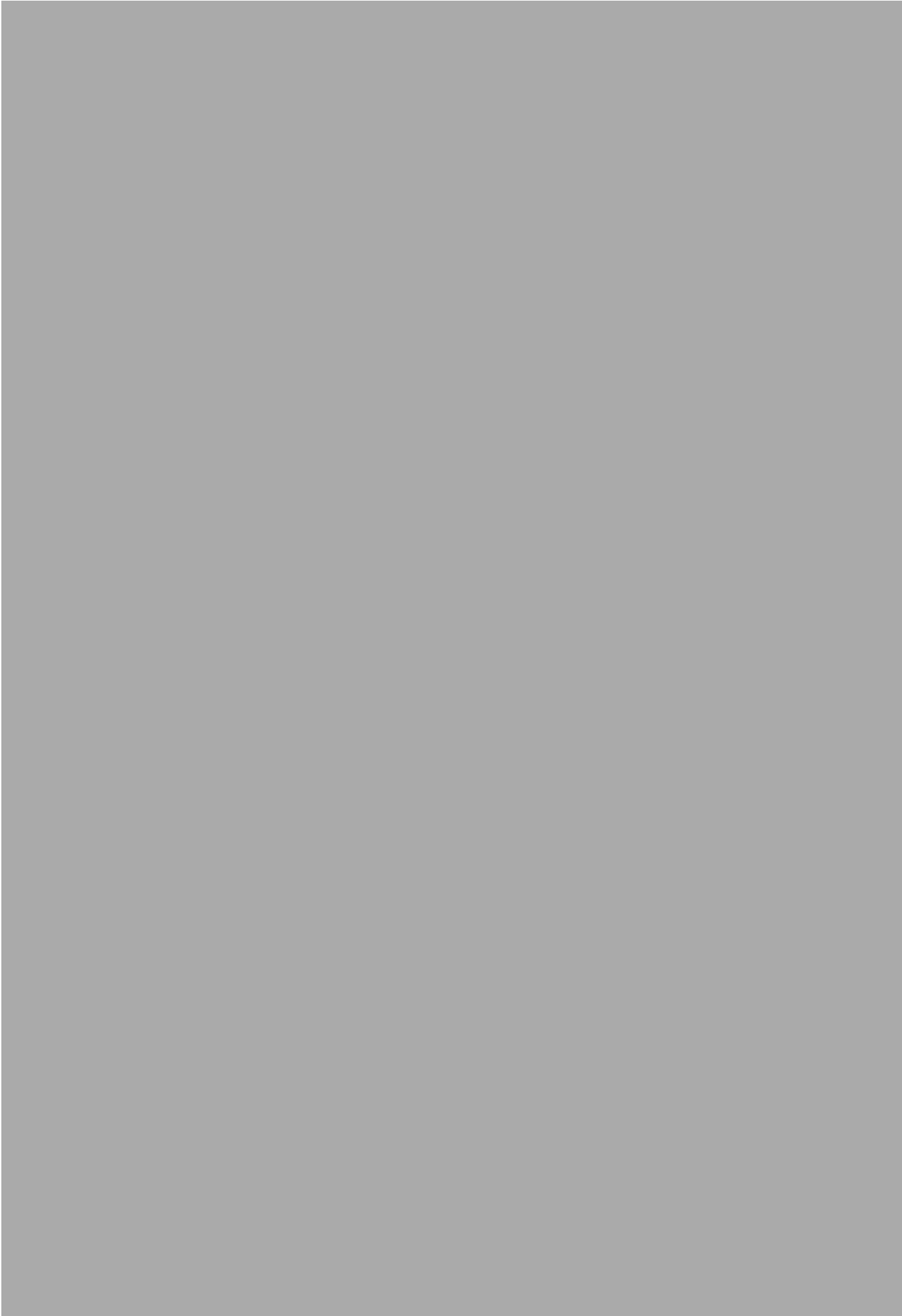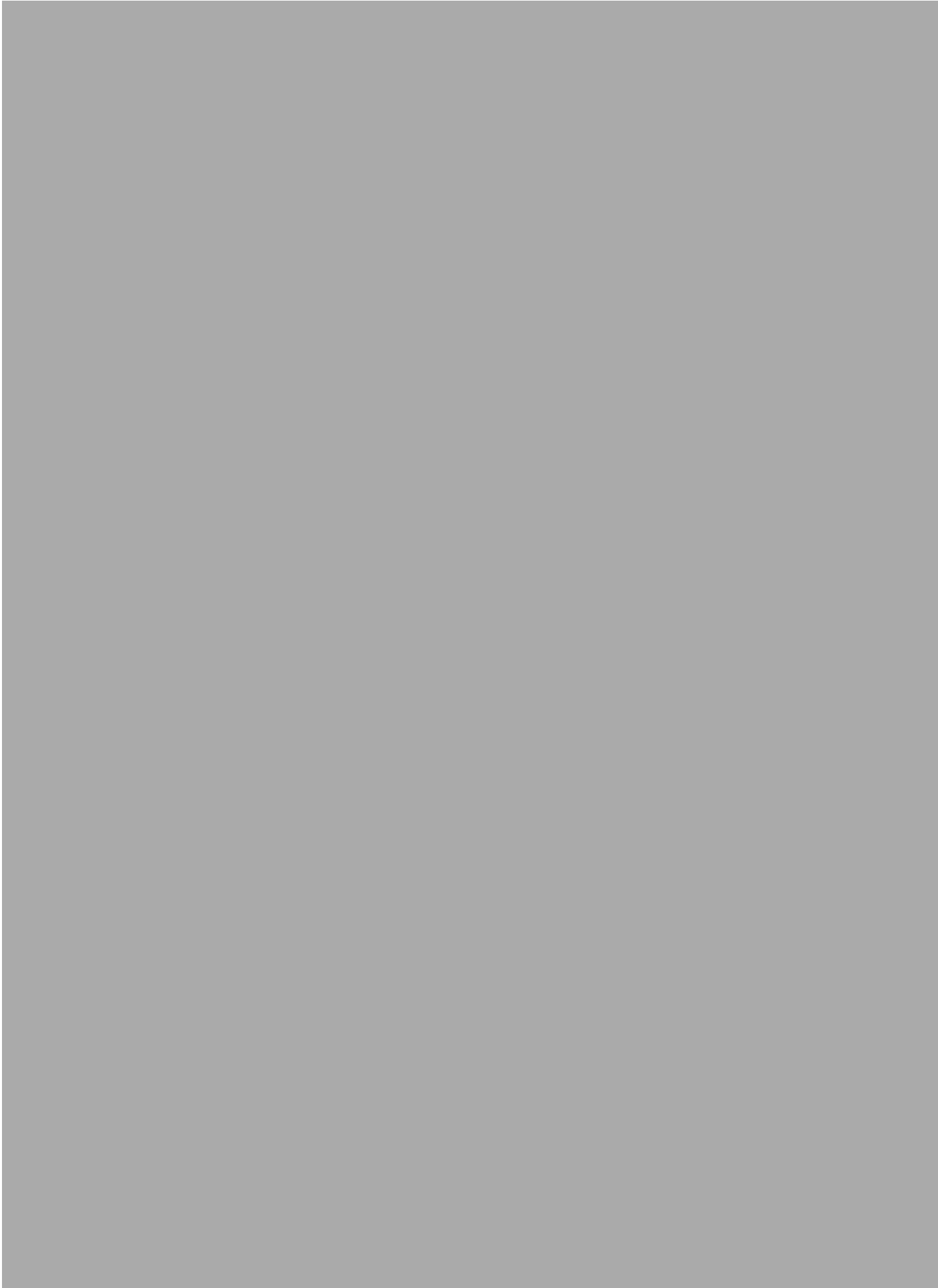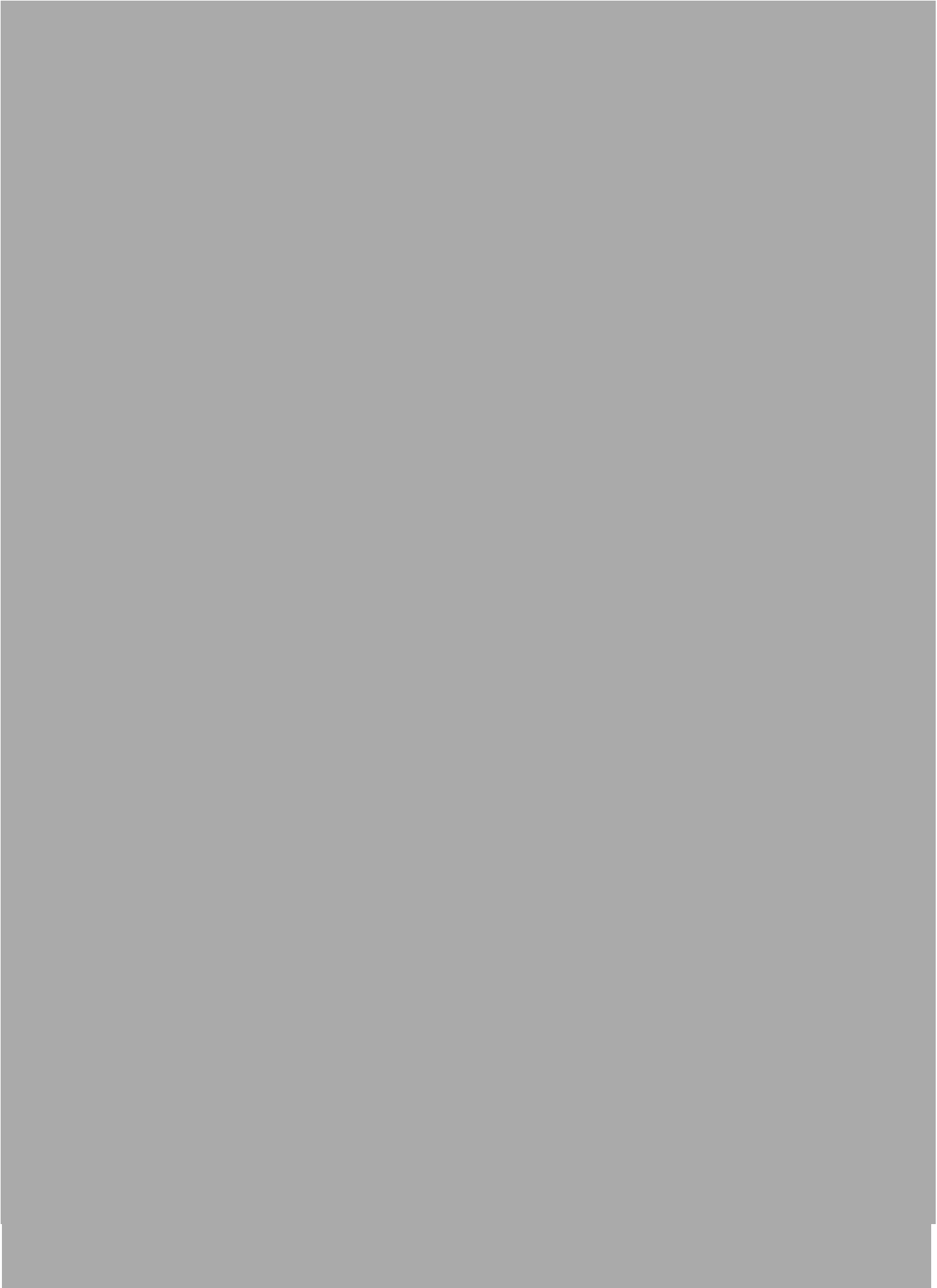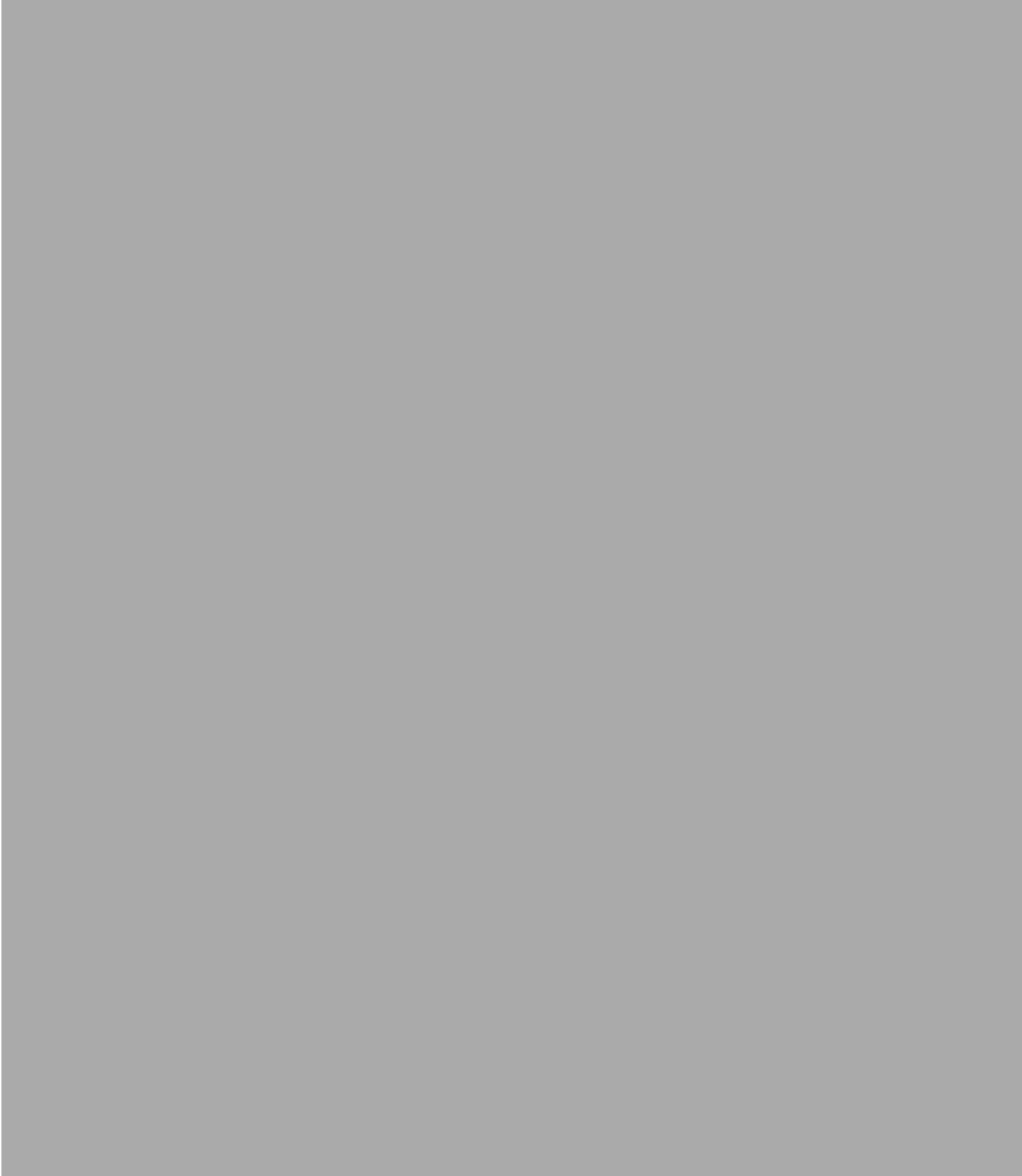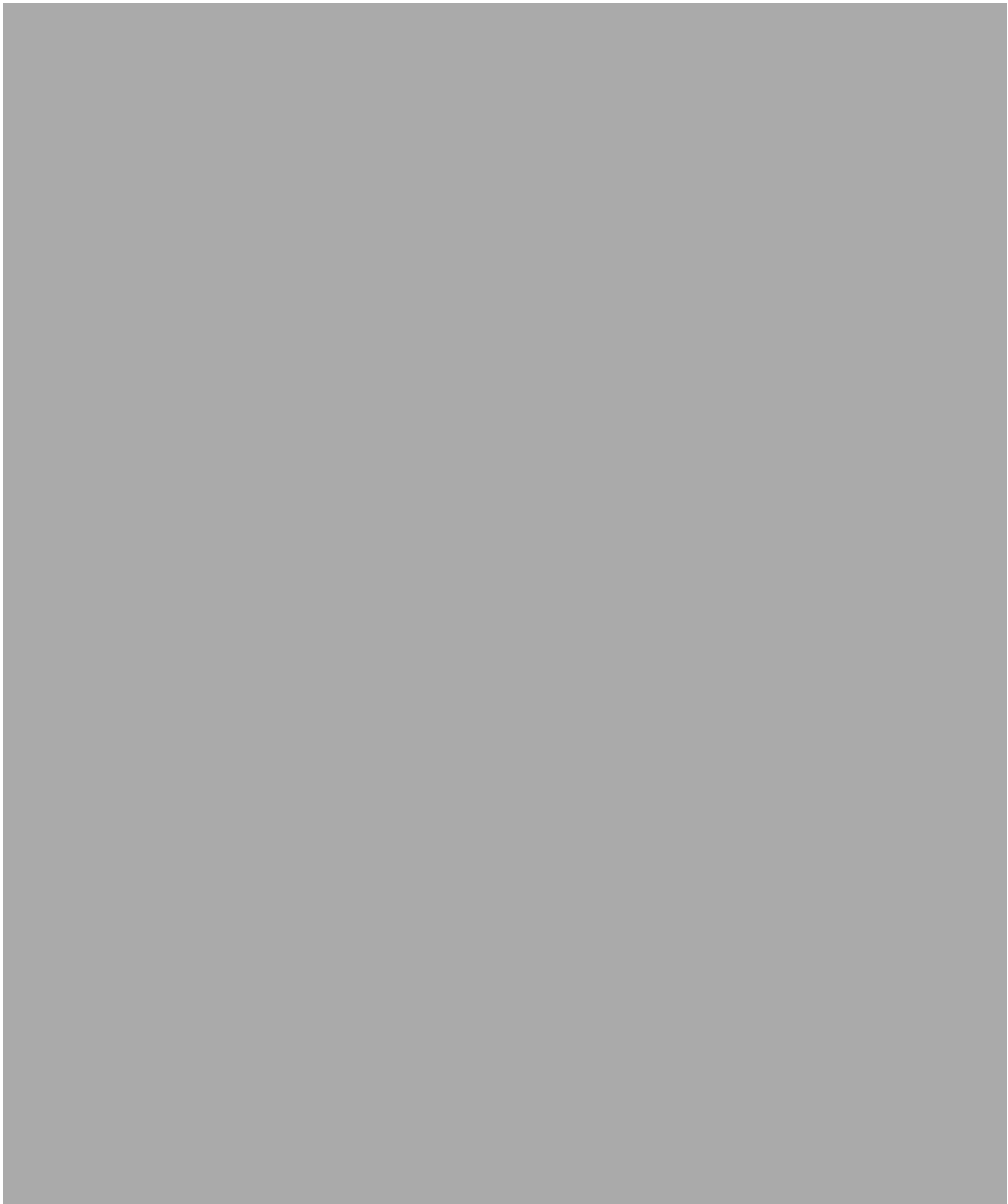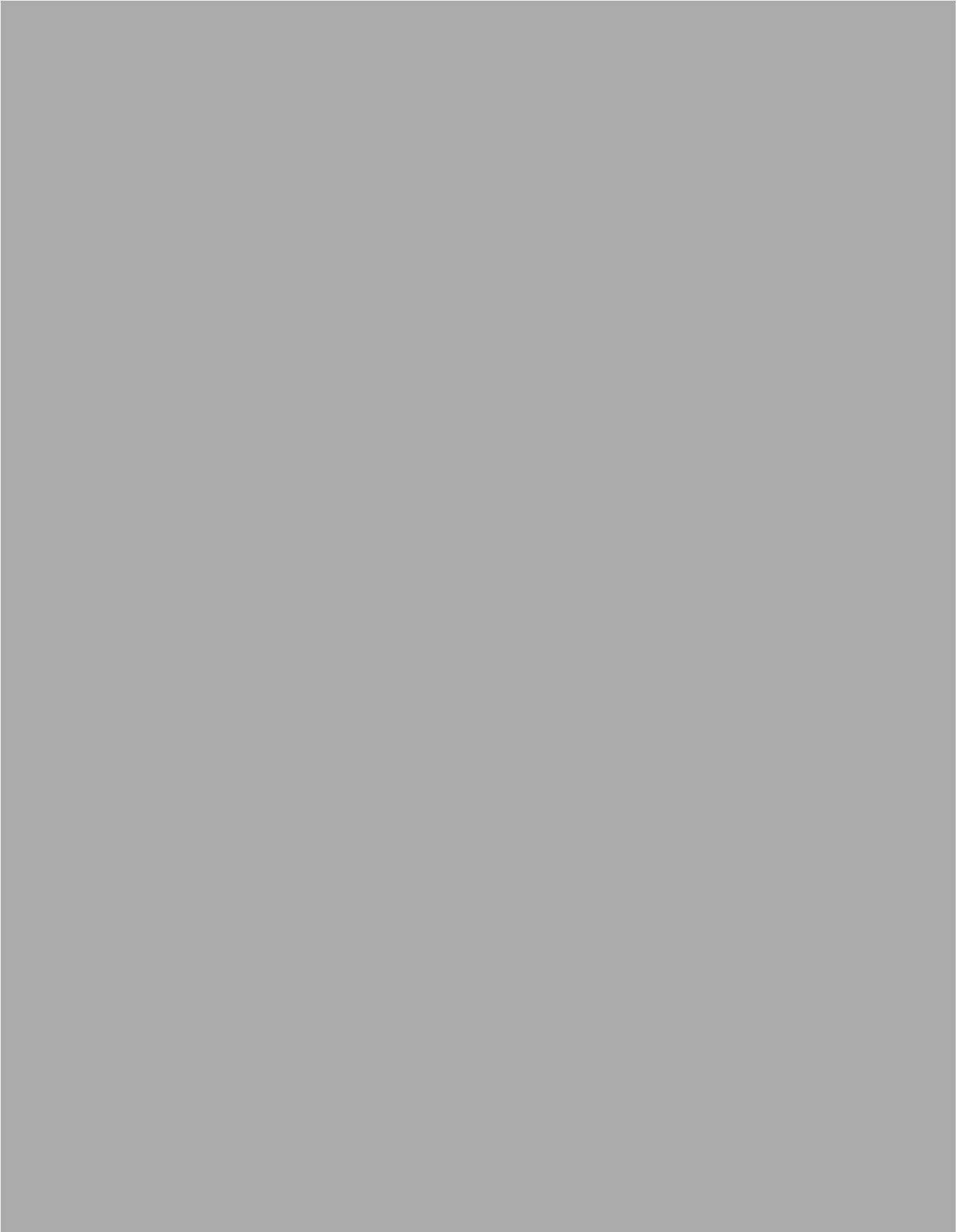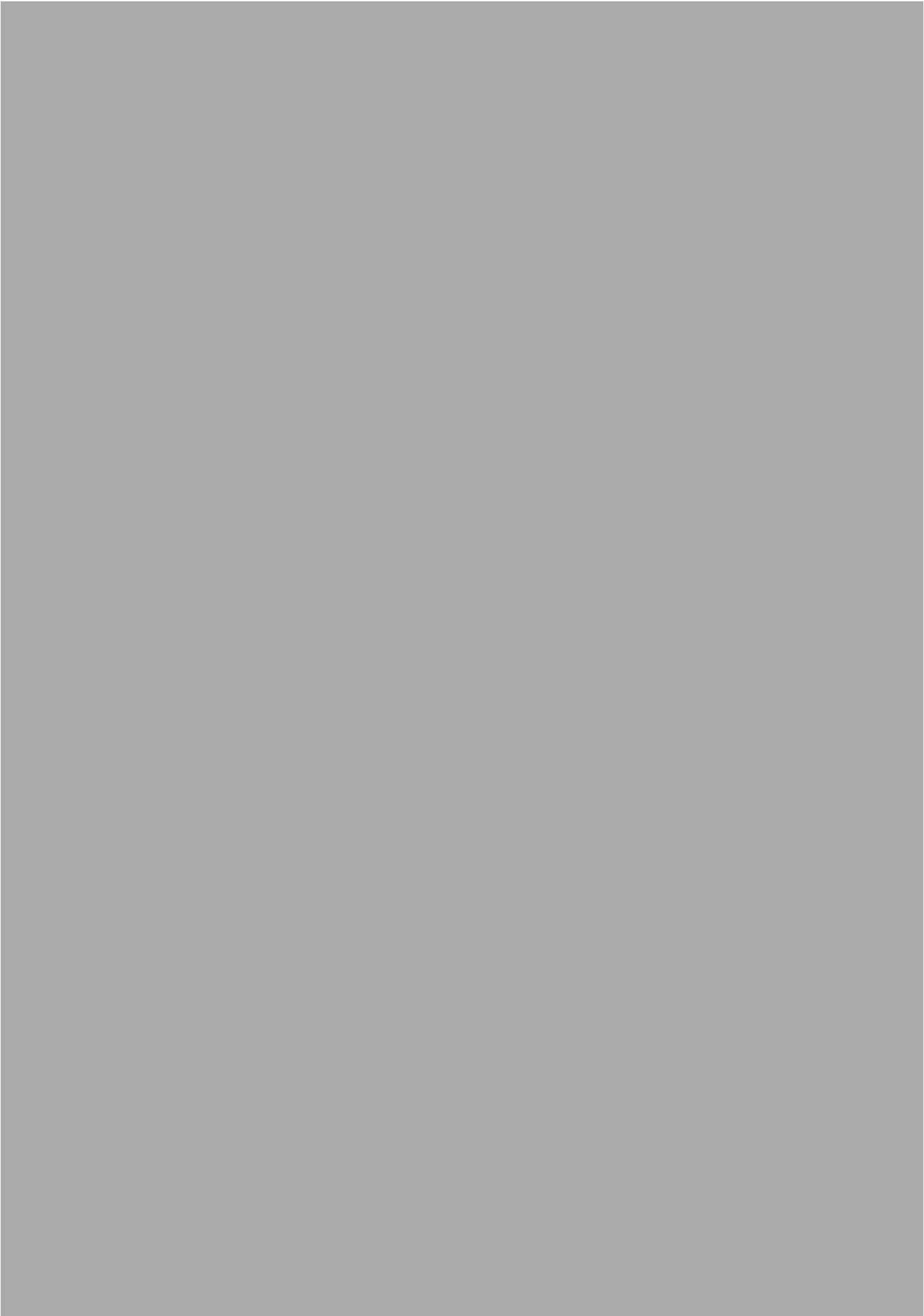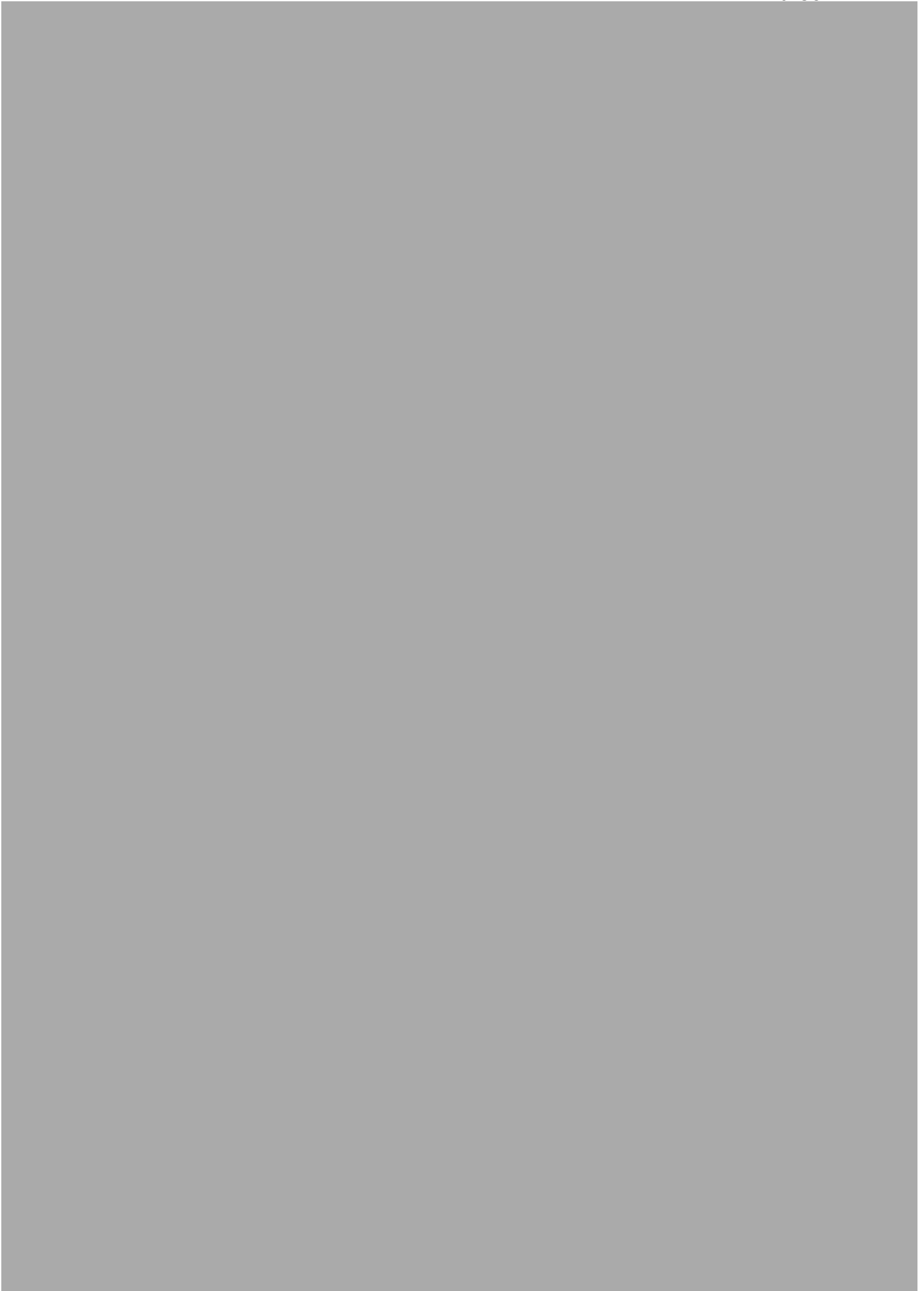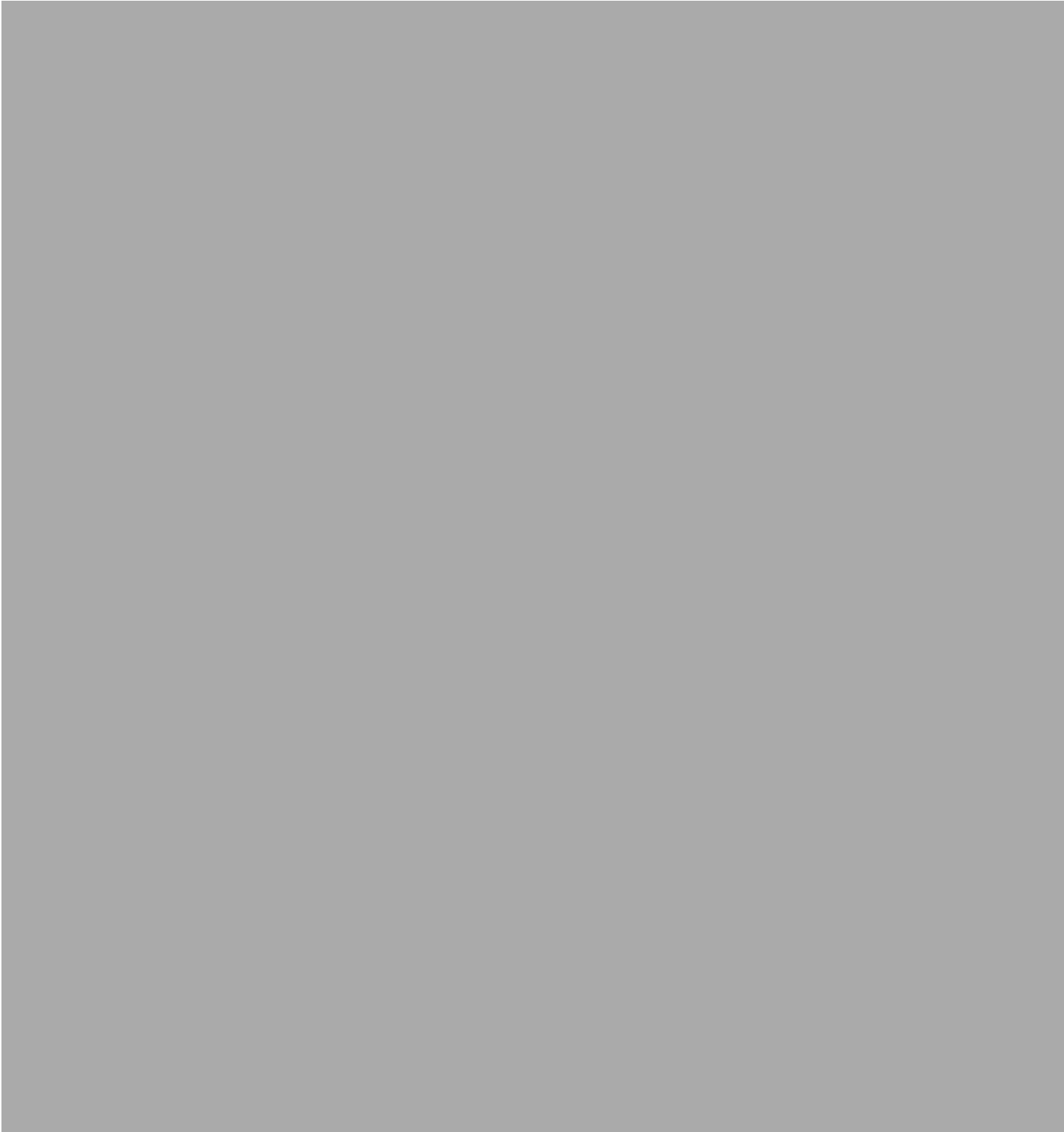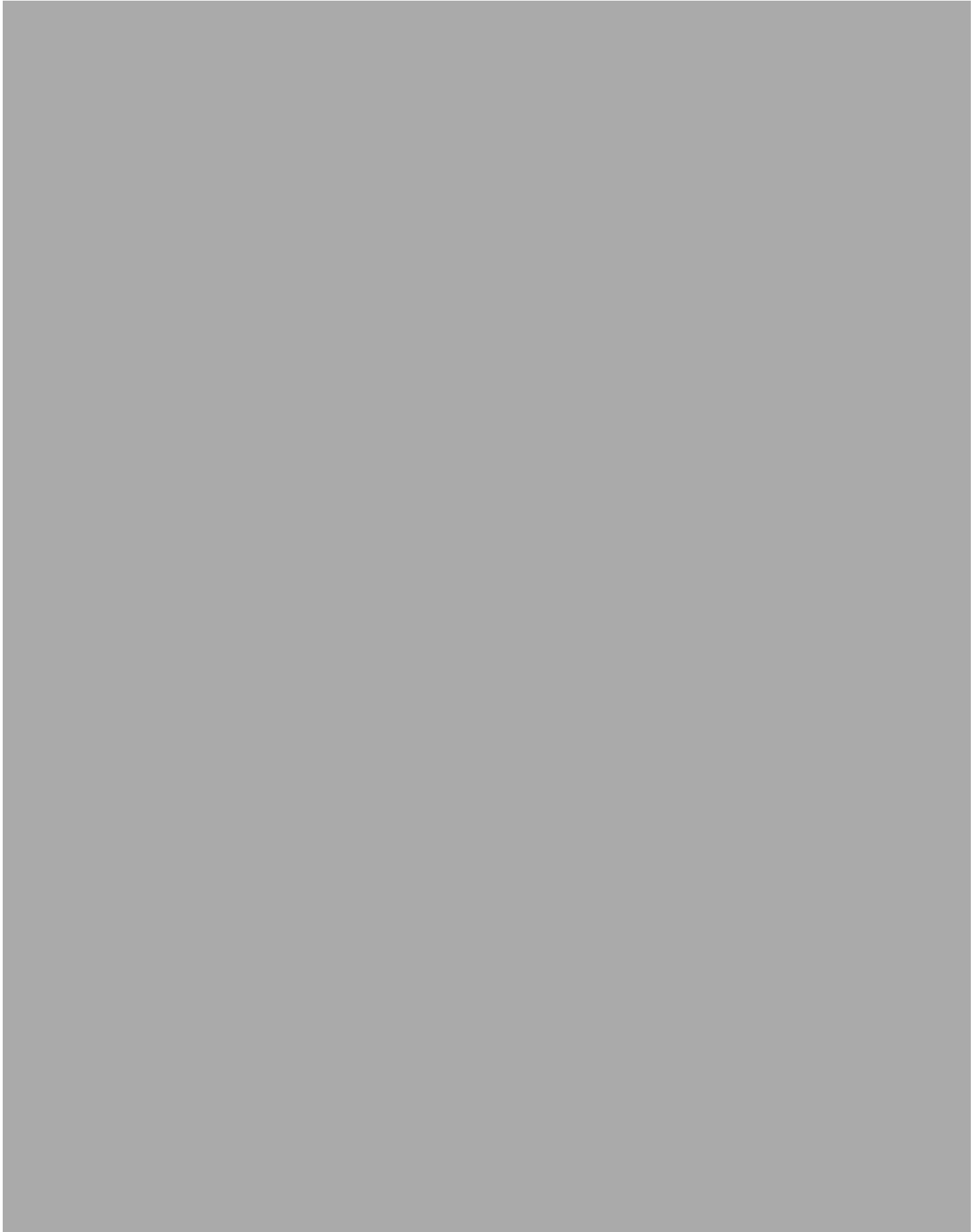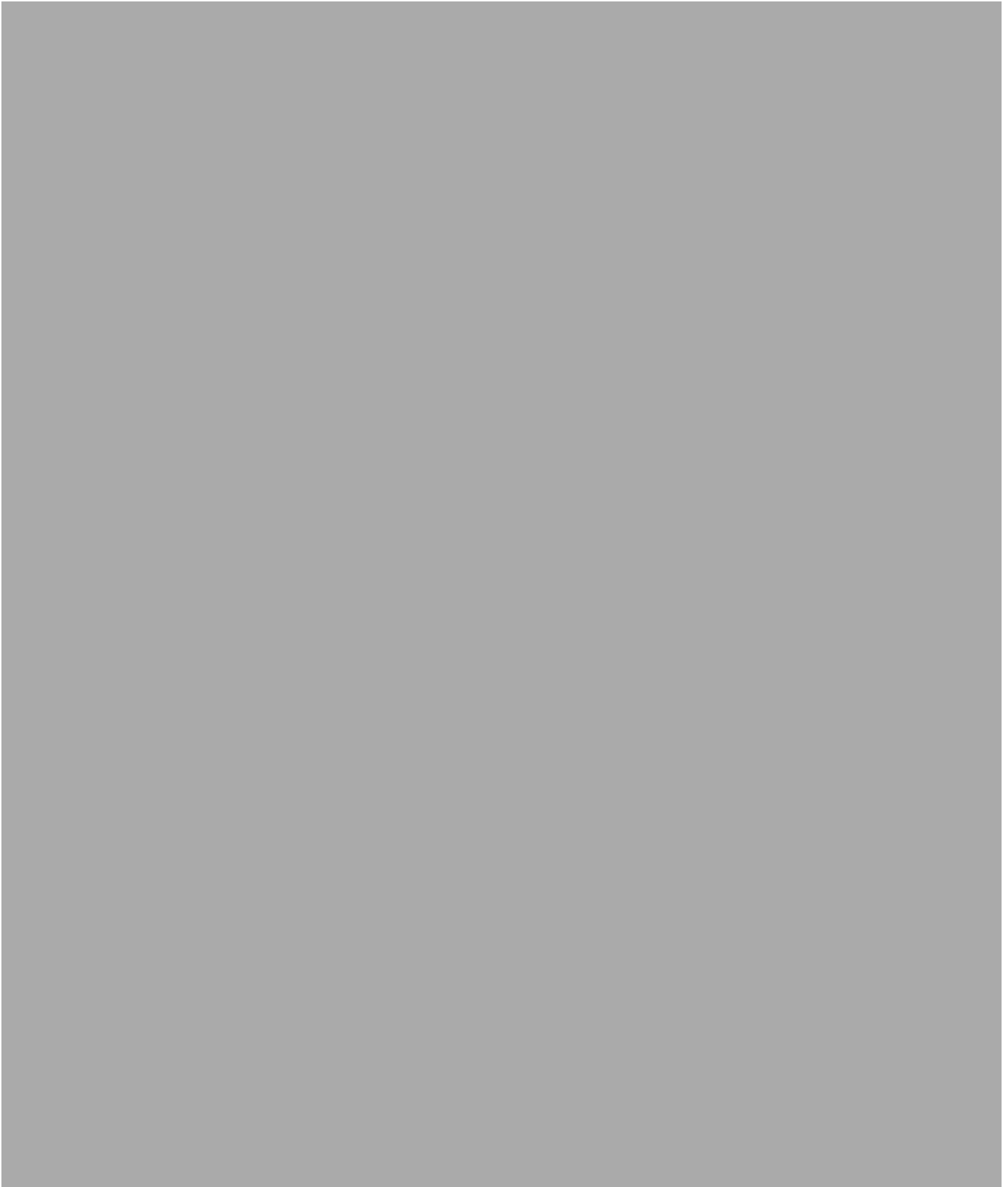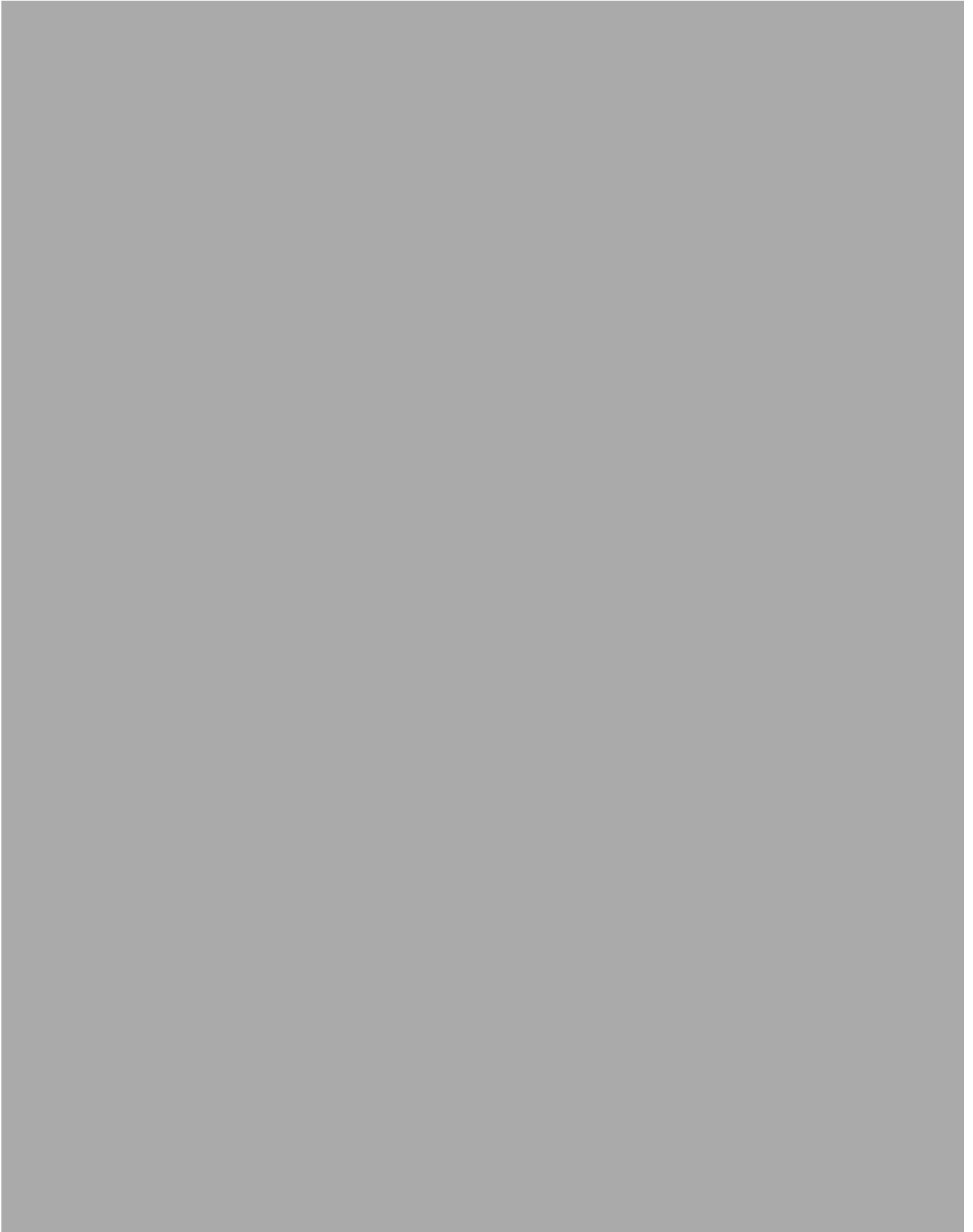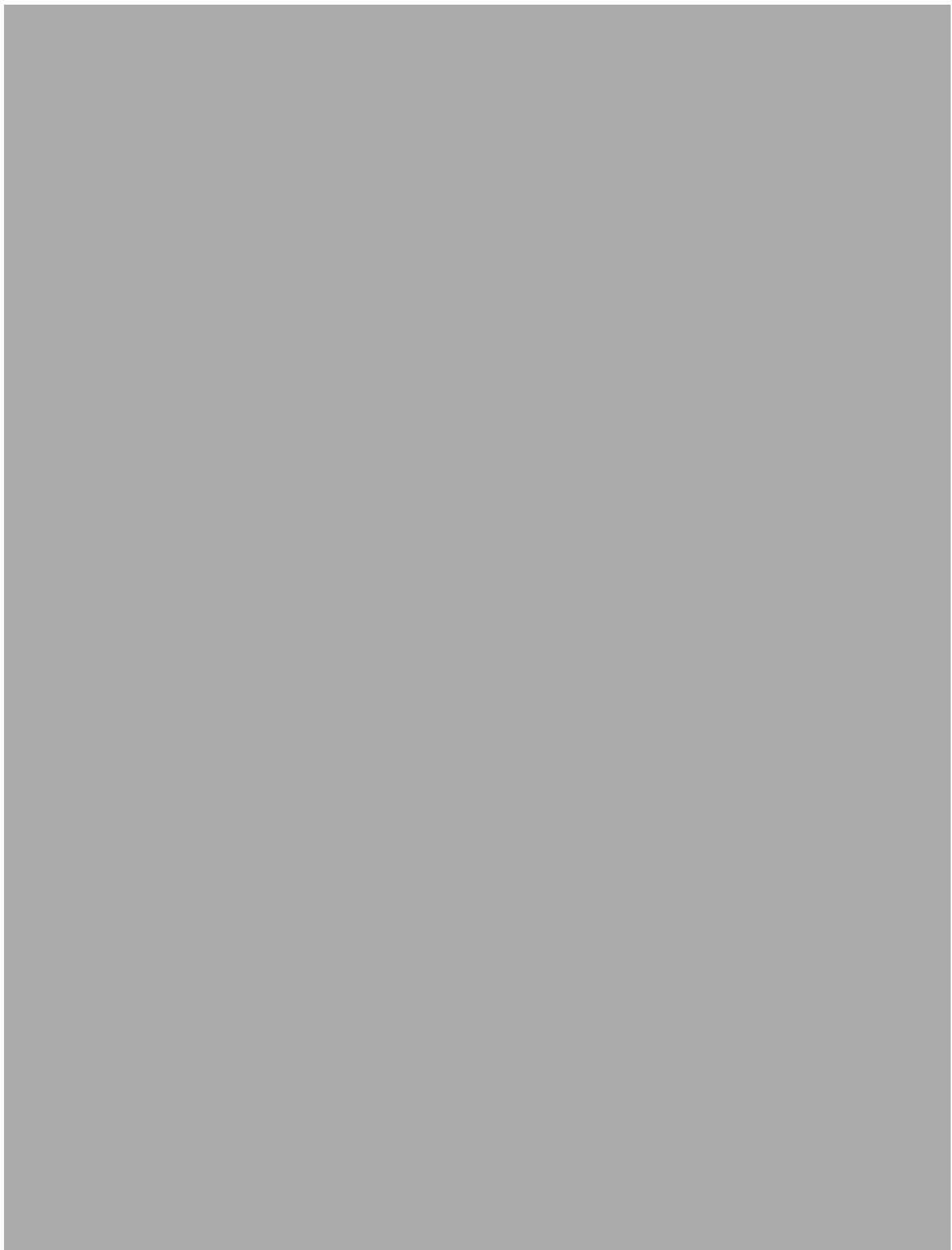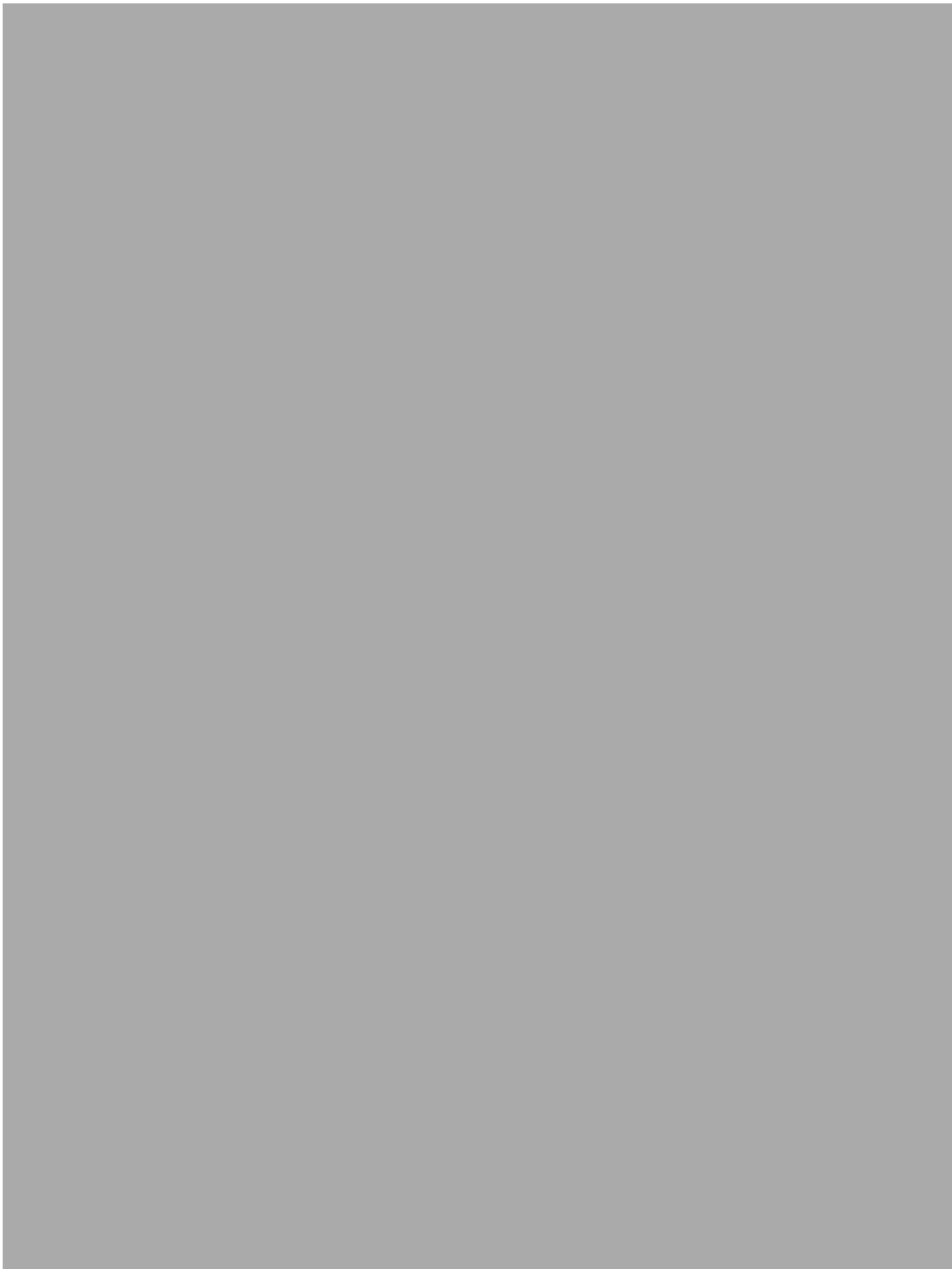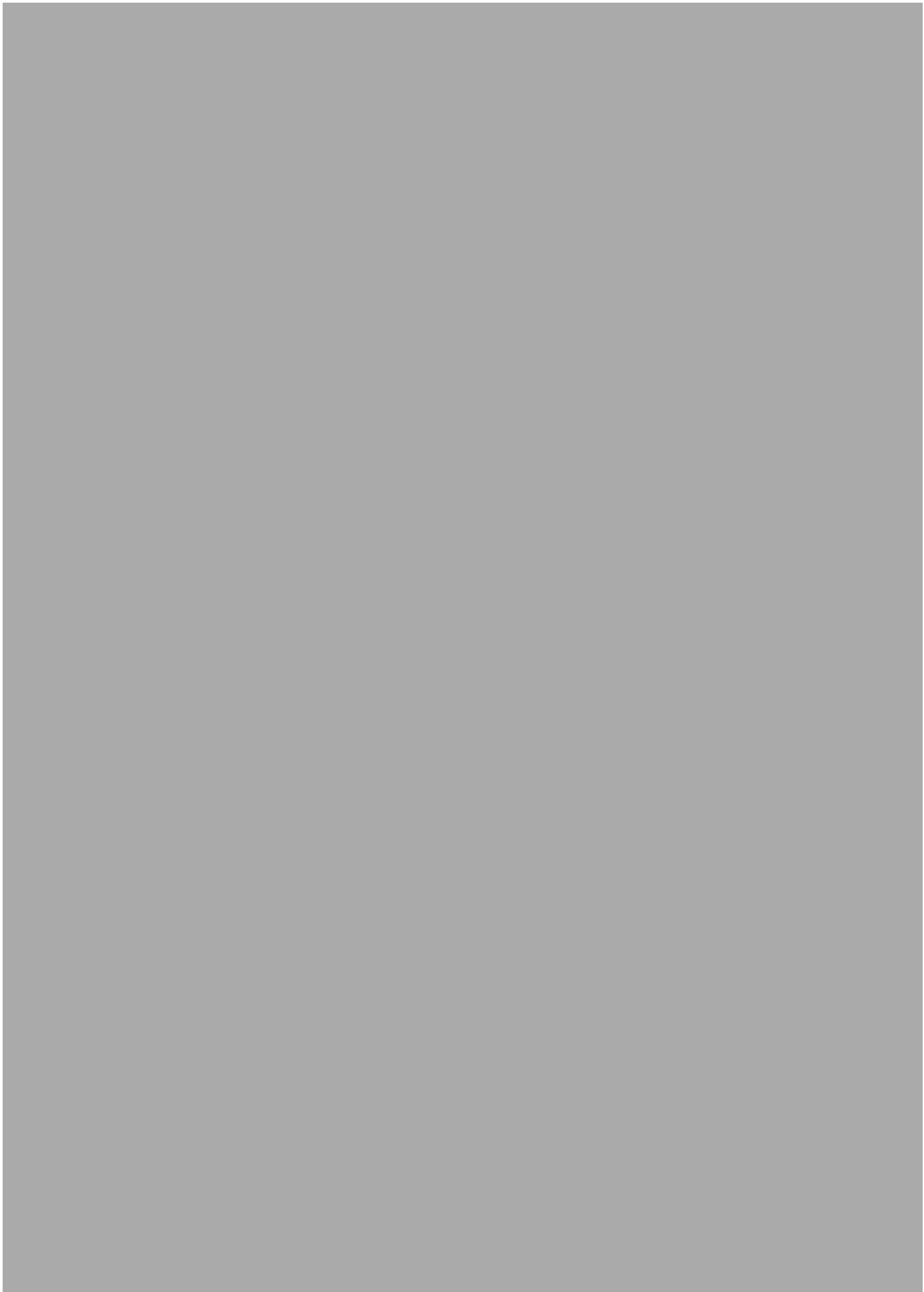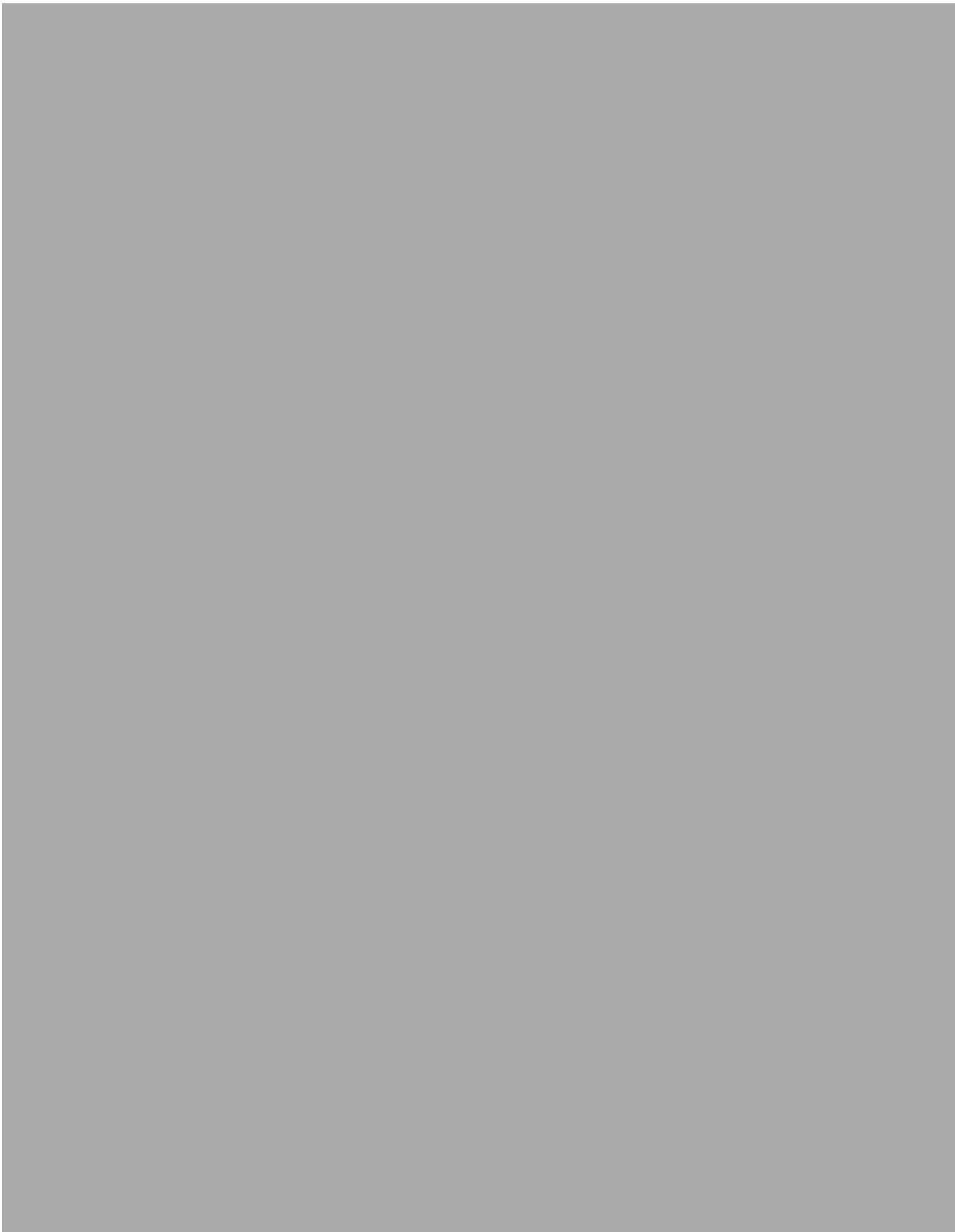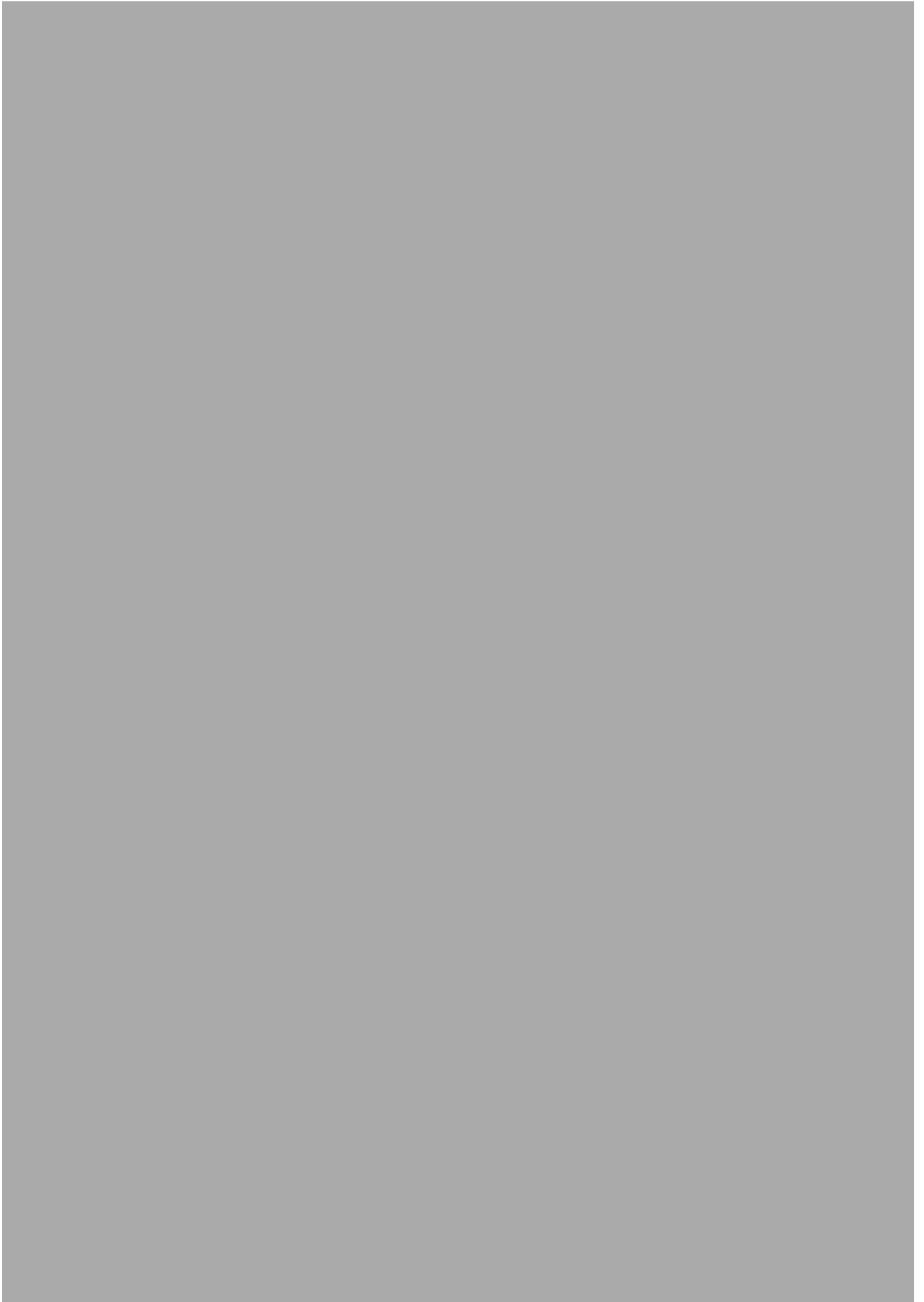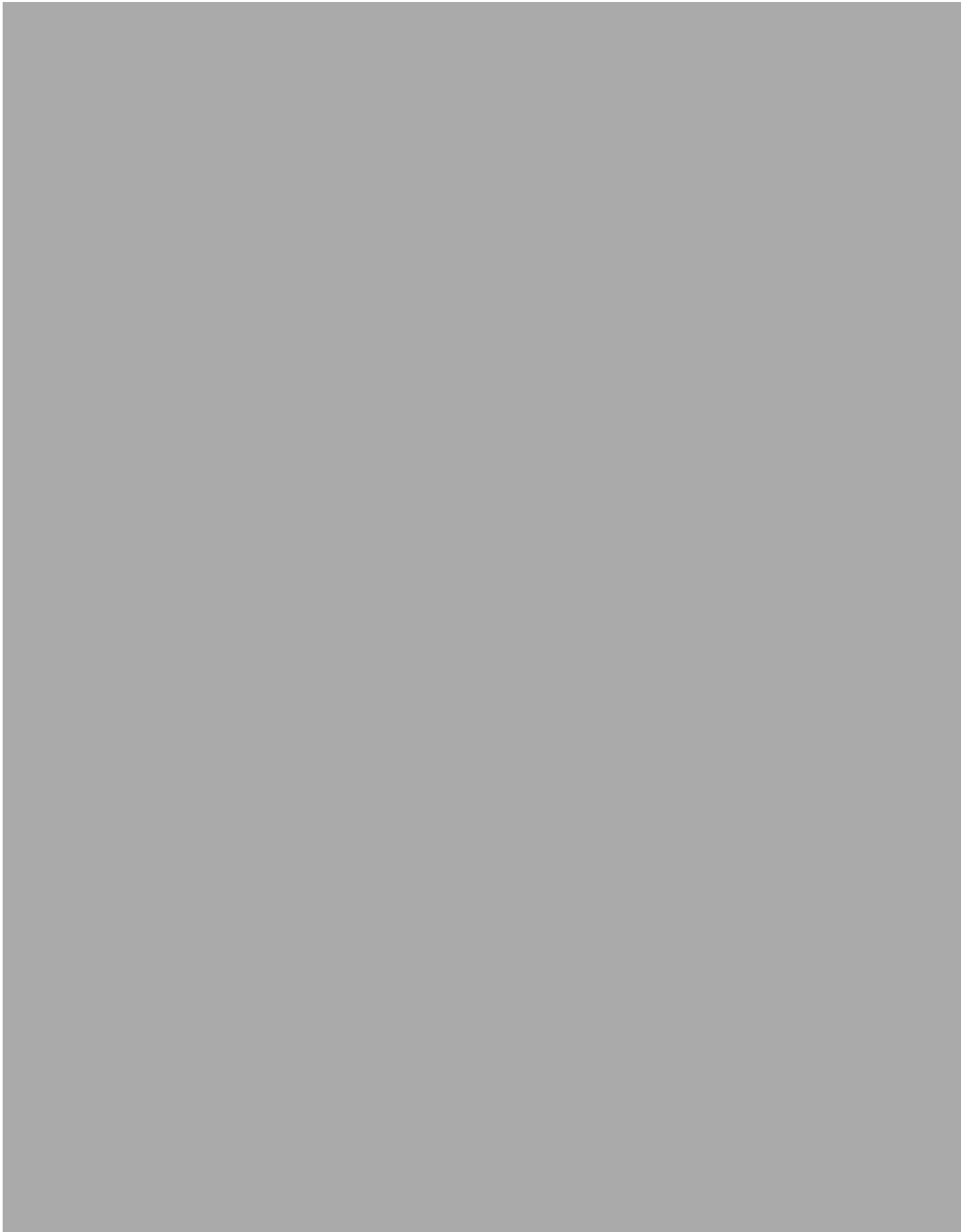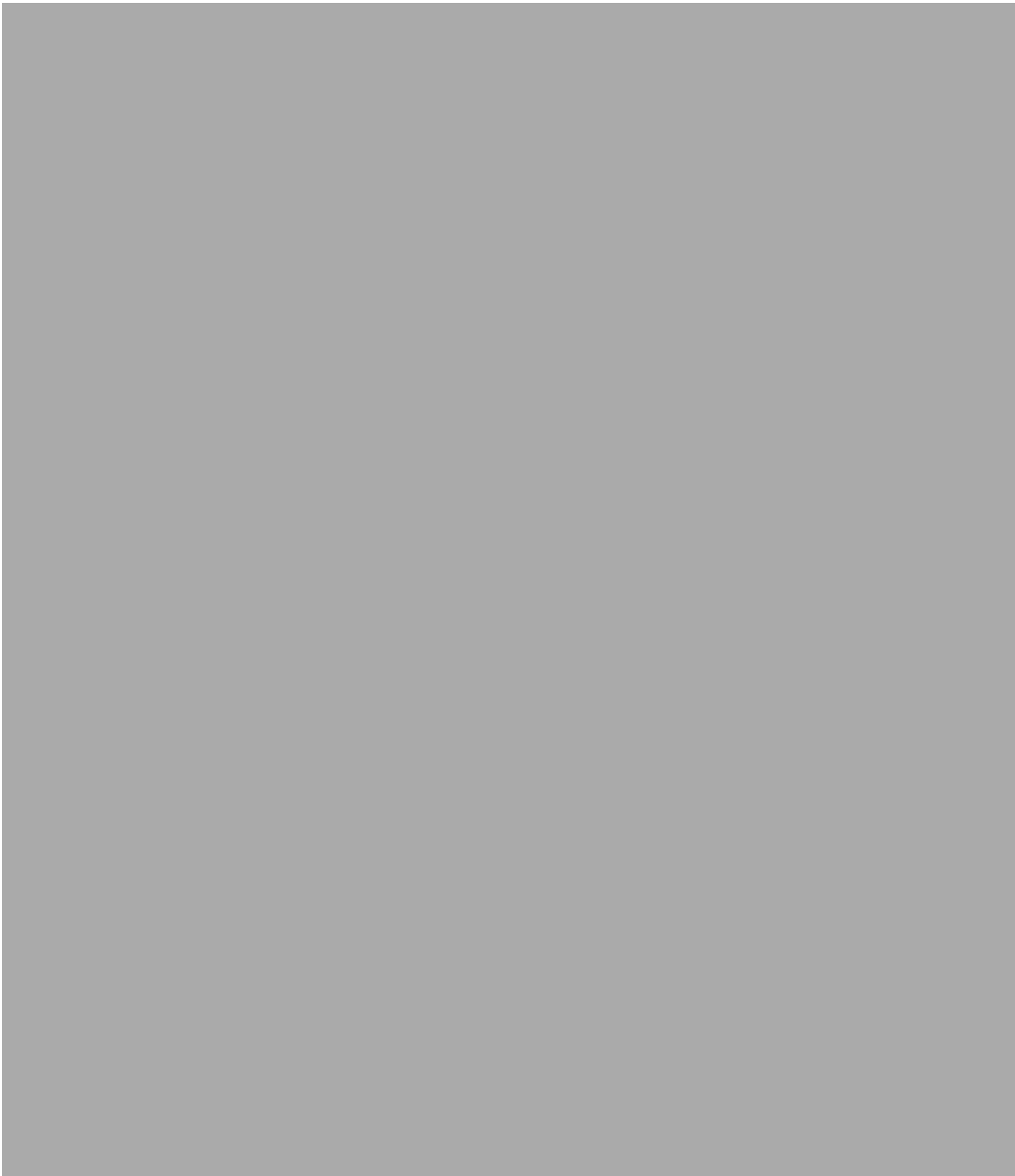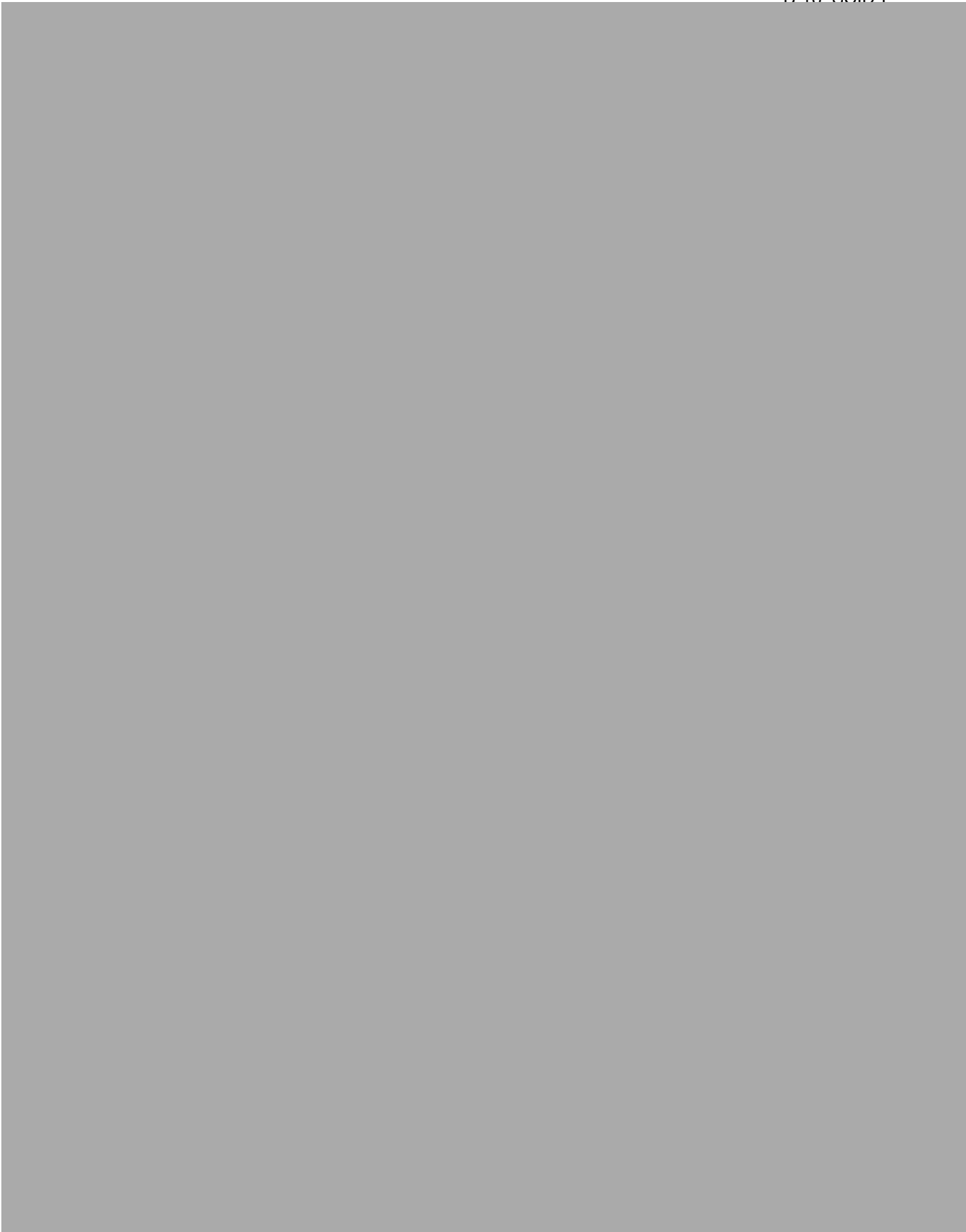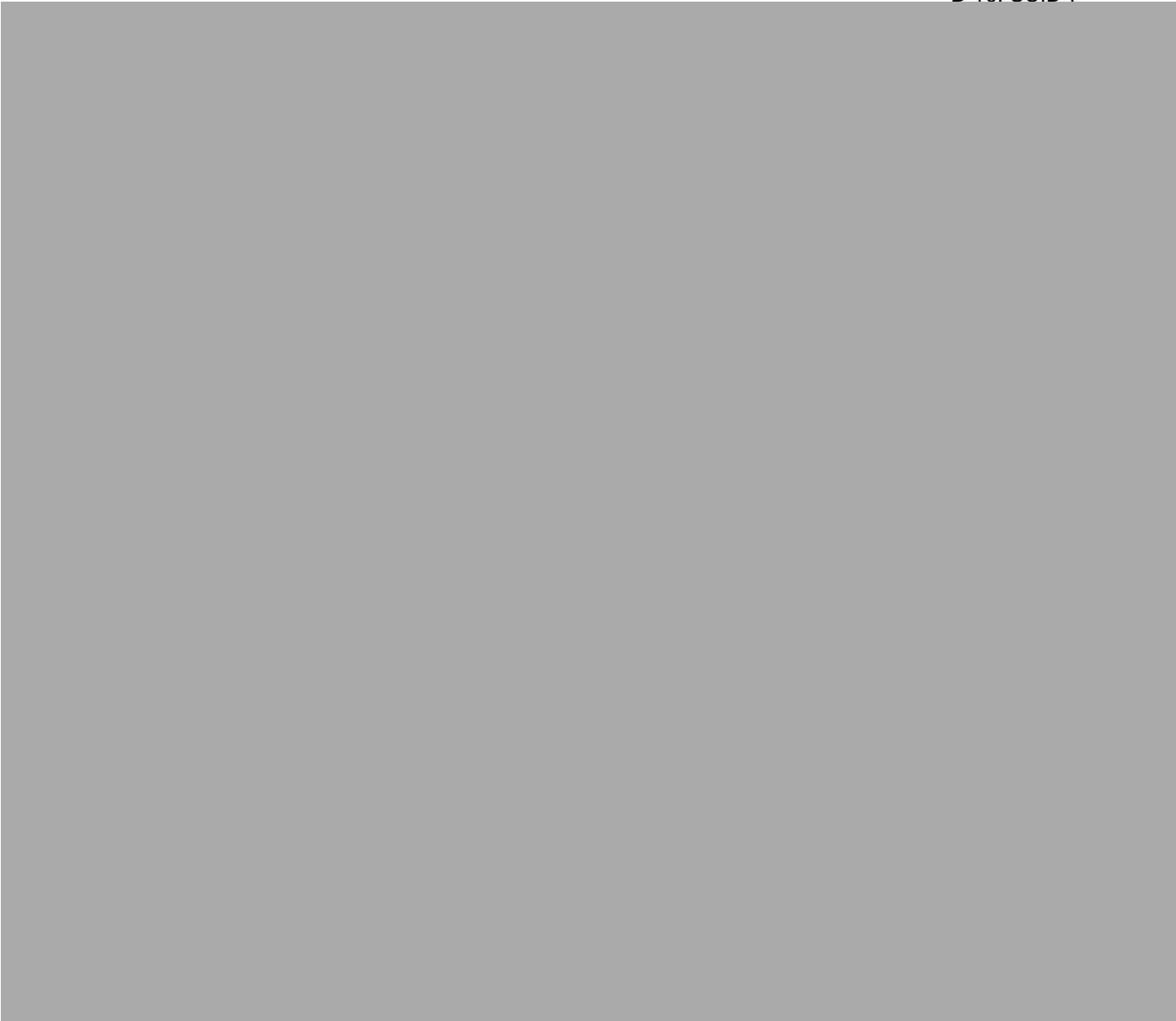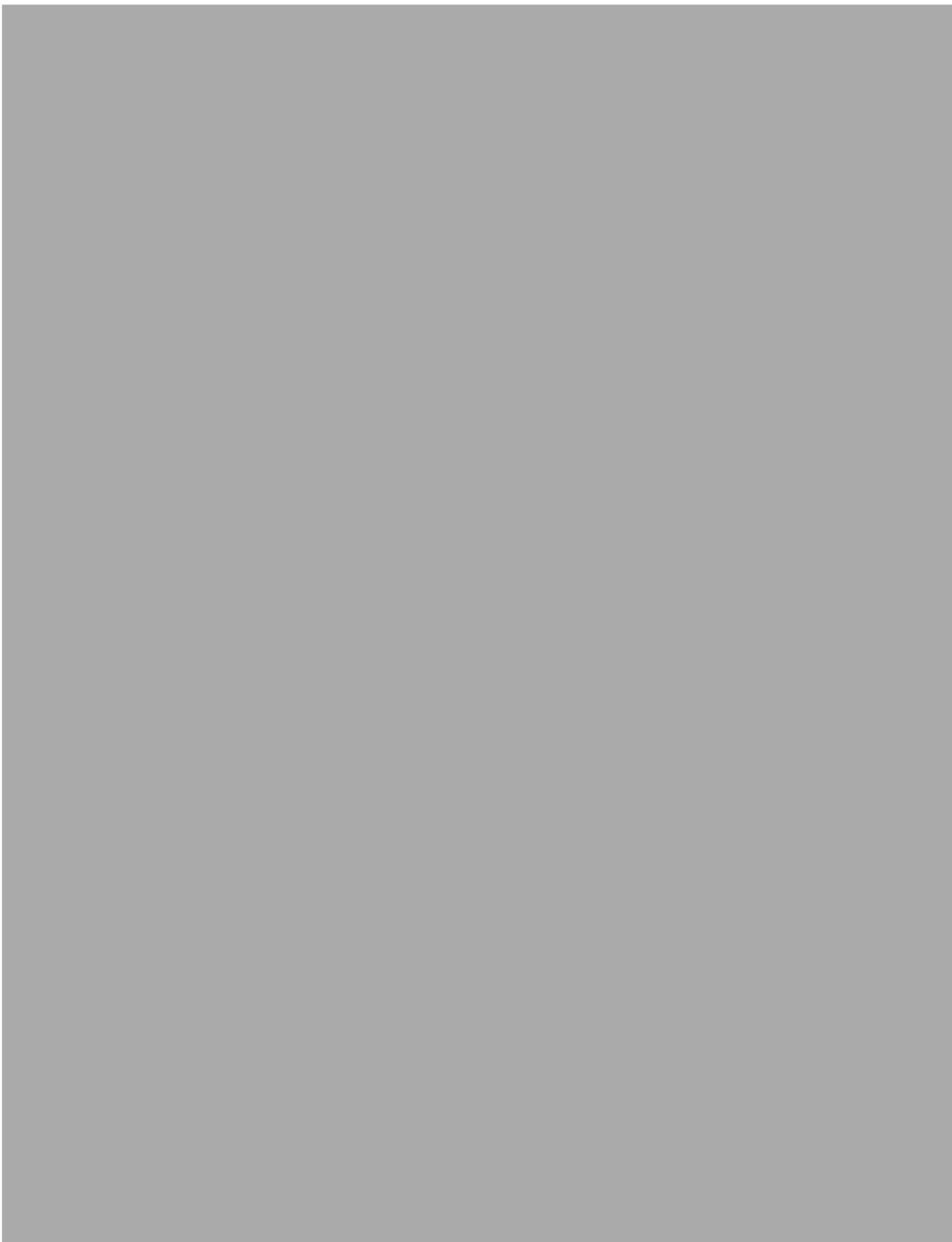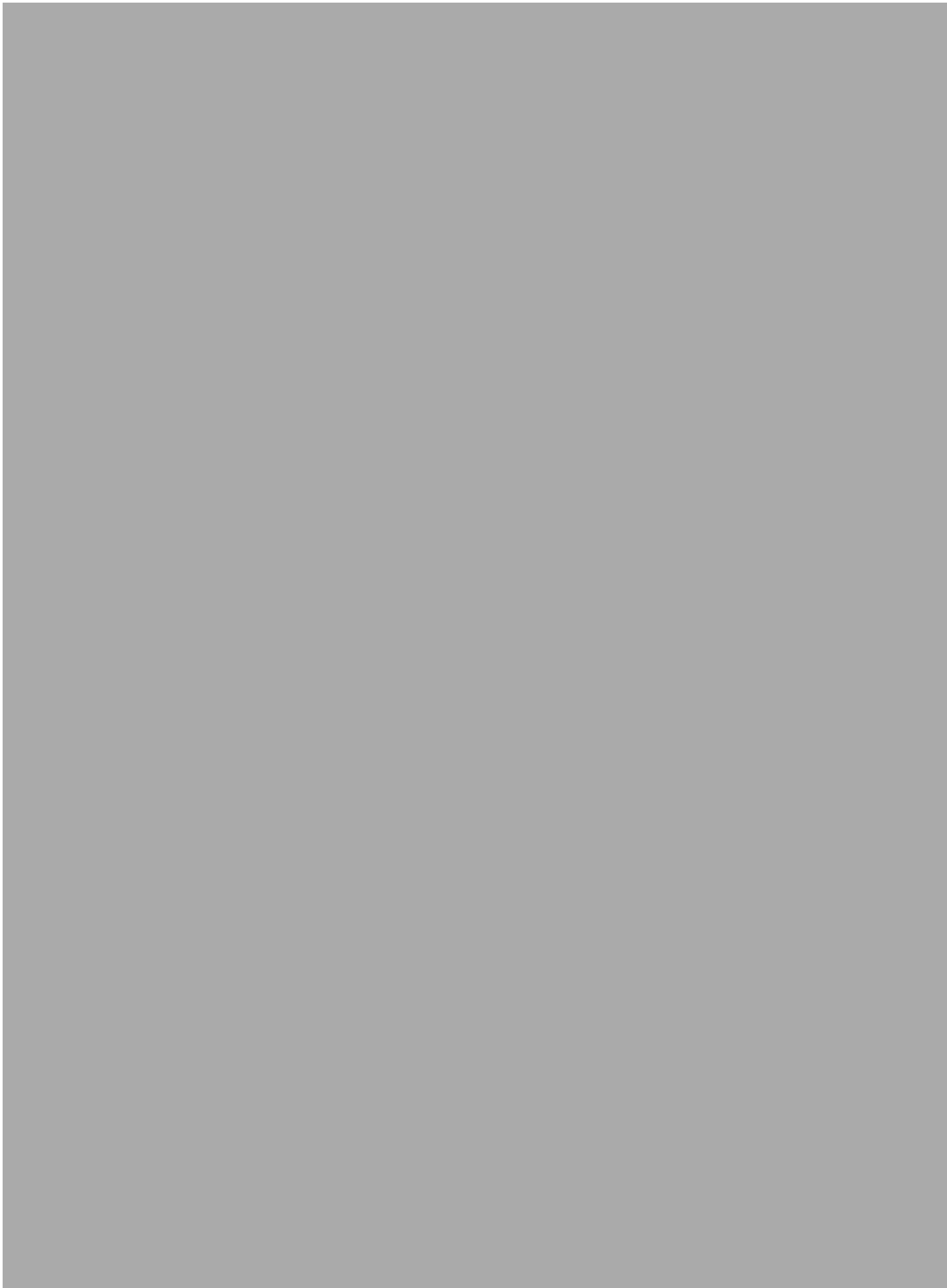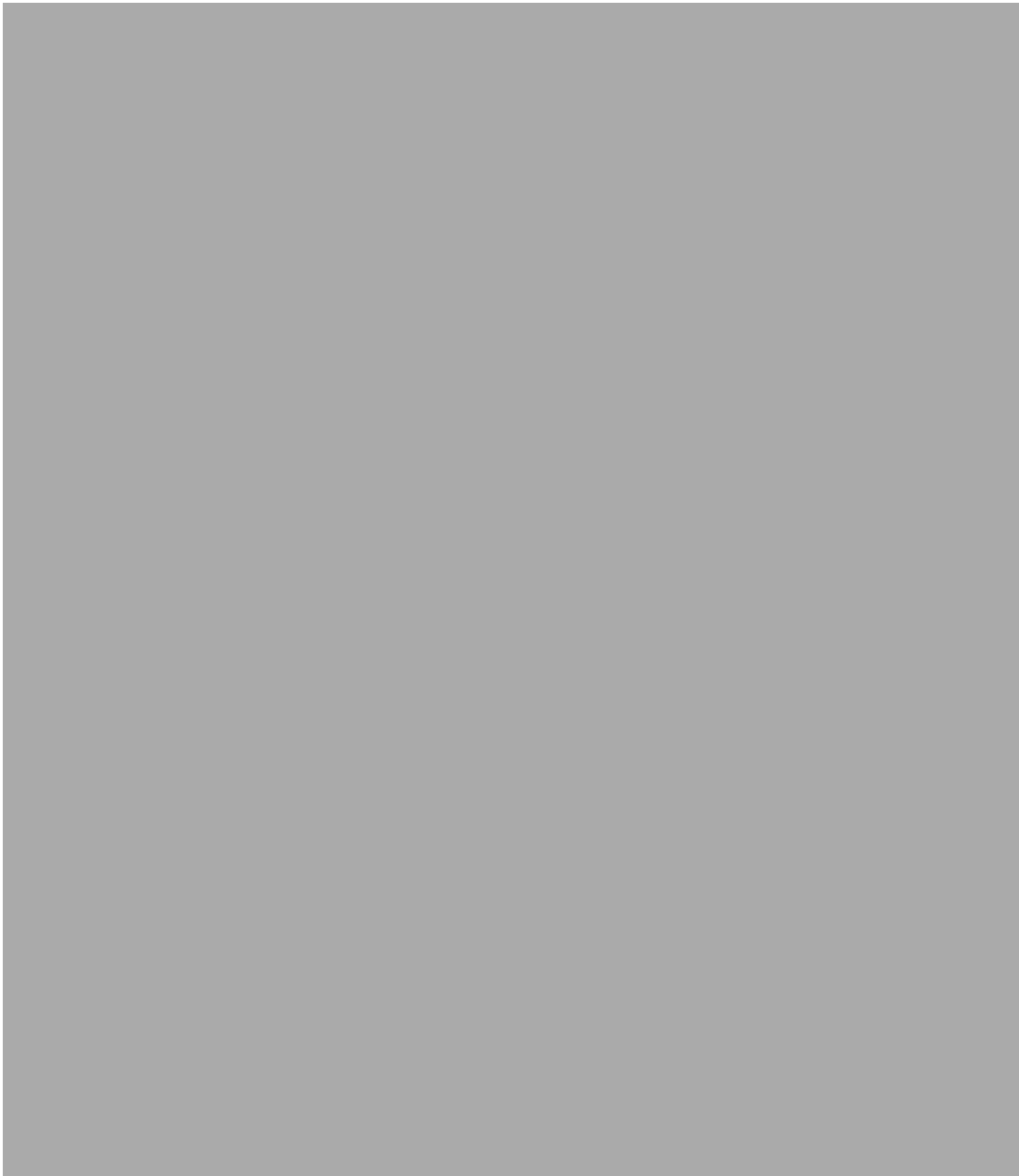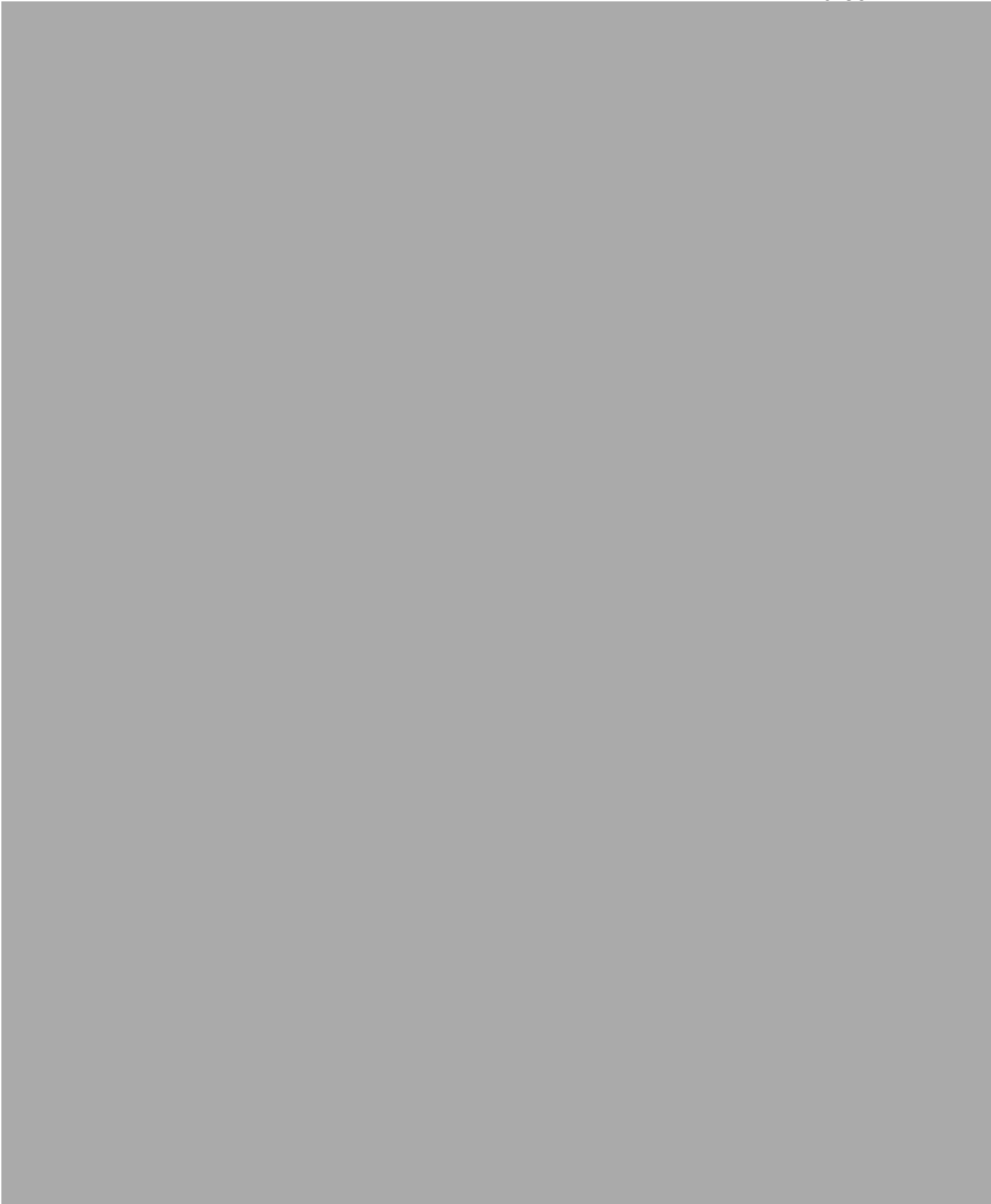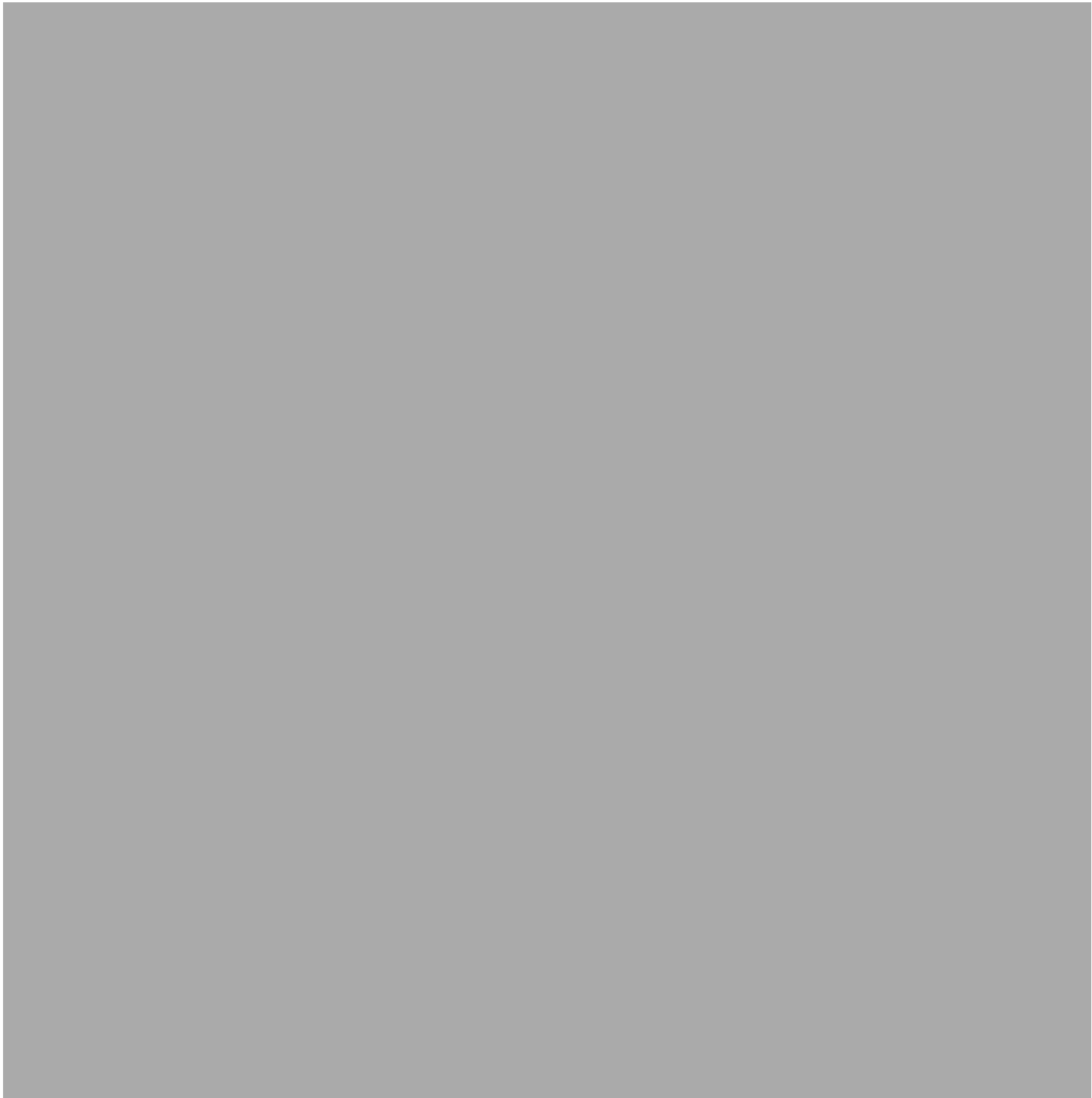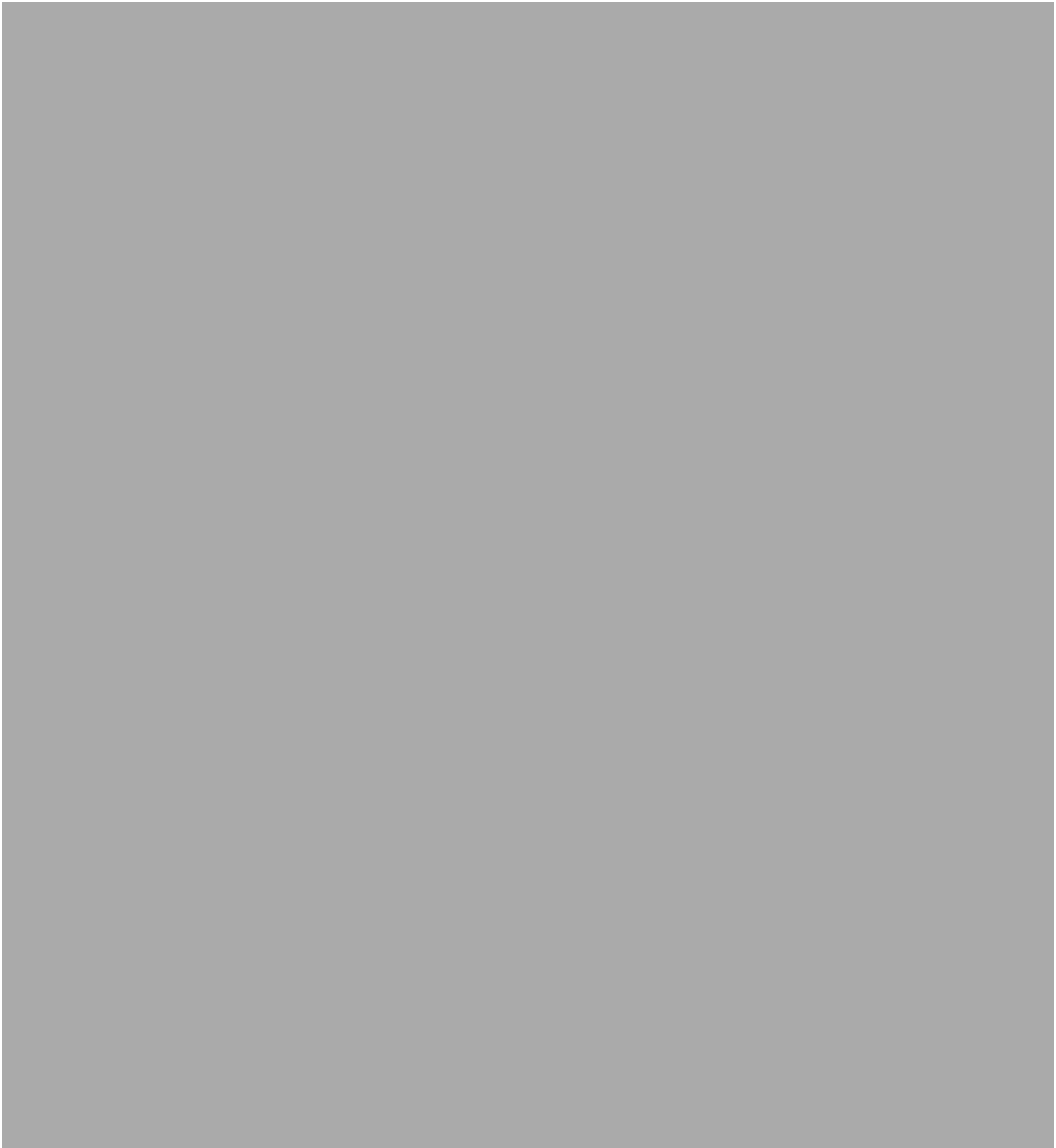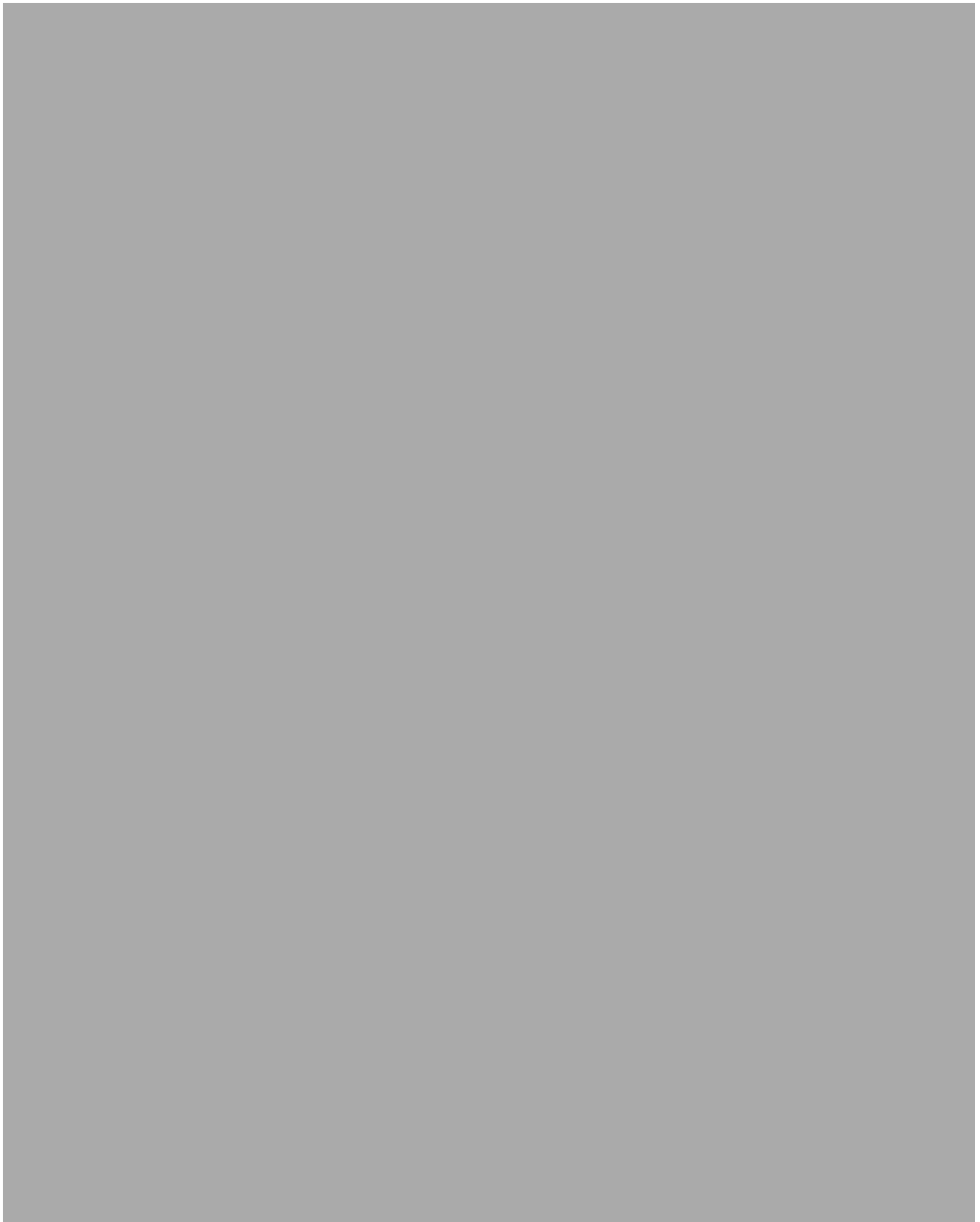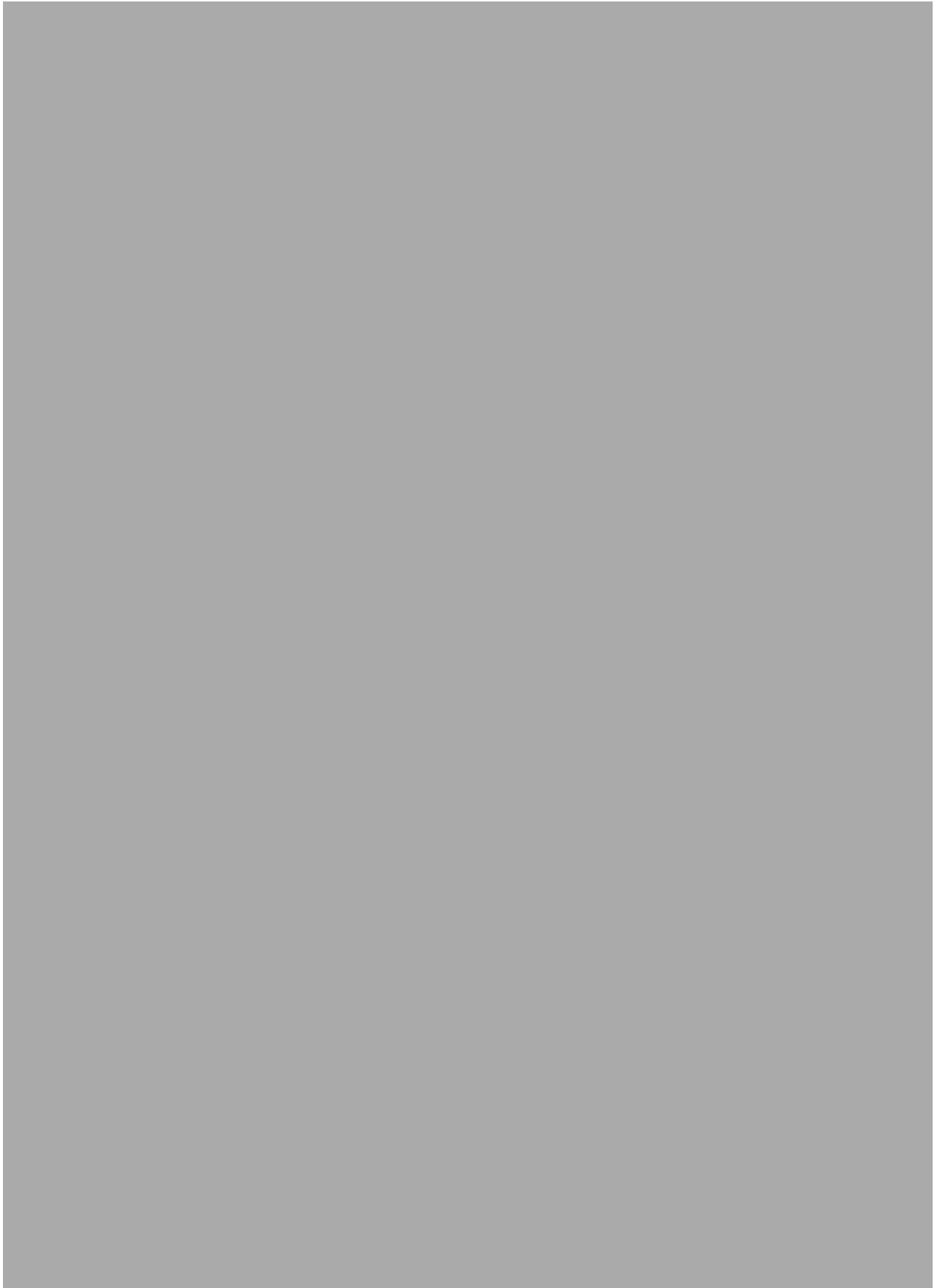
Screening for the hair steroid analysis

Natural hair colour	
Curls:	no ☐ yes ☐
Hair washes per week	
Hair treatments *(colour, perm, etc.)*	no ☐ yes ☐ *if yes → type and date:* ....
Hair care products *(shampoos, conditioner, spray, etc.)*	*type & frequency* ....
Medication intake *(other than for mental health, including oral contraceptives)* *(during the past 12 months)*	no ☐ yes ☐ *if yes → name, dose and intake since:* ....

Additional screening for the MRI session

Documented head injury *(including unconsciousness)*	*no* ☐ *yes* ☐ *if yes → details:* ....
Neurological disorders	*no* ☐ *yes* ☐ *if yes → details:* ....

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Name: _____

ID: _____

DOB: ____/____/_____

Registration number: _____

Exam card: _____

Time in: _____

Time out: _____

Handedness: ☐ left ☐ right

☐ ambidexterity

Scan order

_____

_____

_____

_____

_____

_____

_____

_____

_____

Comments

_____

_____

_____

_____

_____

Slices: ____

Voxels: _____ x _____ x _____ mm

TE: _____ ms

TR: _____ sec

Dummy scans: ___

n-back dynamics: _____

faces dynamics: _

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